Clinical Study Protocol	
Drug Substance	Sodium Zirconium Cyclosilicate (SZC)
Study Code	D9485C00001
Version	3.0
Date	23 March 2021

A Phase 3b, Multicentre, Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Reduce Incidence of Pre-Dialysis Hyperkalaemia with Sodium Zirconium Cyclosilicate in Chinese Subjects (DIALIZE China)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): Not applicable

VERSION HISTORY

Version 3.0, 23 March 2021		
Section	**Summary of change**	**Reason for Change**
Section 1.1 **Table 1** **Table 2**	Remove the Day of the week. M/T: Monday/Thursday; W/Th: Wednesday/Thursday; F/S: Friday/Saturday	This rule is not consistent with China clinical practice and limits the enrolment.
Section 1.1 **Table 2**	Concomitant medication: select in V8, V11, V13, V15, V17, V19 and V21.	To clarify the requirement that concomitant medication needed to be checked on every visit.
Section 1.2	Study Period: update the estimated date of first subject enrolled and last subject completed.	Based on the actual enrolled date of first subject.
Section 1.2 **Section 9.4.1.3** **Section 9.4.1.4**	The wording "non-linear" was replaced by "generalized linear"	To be more precise description for the analysis model.
Section 5.3.5	Remove the wording "MWF or TTS". "MWF or TTS" instead of Monday/Wednesday/Friday or Tuesday/Thursday/Sunday.	To be consistent with section 1.1
Section 5.4	Add the statement: "Subjects who cannot complete the screening process due to sample issue is not considered screening failure, sampling or full screening can be postponed to a later time as applicable."	Subjects should not be counted as screening failure due to sample issue.
Section 6.1.2	"If at any time during the study a potassium value (iStat, c-Lab or local lab) measured on a non-dialysis day or pre-dialysis is < 3.0 mmol/L the subject should receive appropriate medical intervention	To make it clearer that study drug should be paused if S-K < 3.0.

	and the study physician should be contacted to discuss further participation of the subject in the study." was changed to "If at any time during the study a potassium value (i-STAT, c-Lab or local lab) measured on a non-dialysis day or pre-dialysis is < 3.0 mmol/L**,** study drug should be withheld and hypokalaemia should be managed as per standard practice. The patient should be evaluated for any intercurrent illness or comorbidity that may increase the risk of hypokalaemia. The study physician should be contacted to discuss further participation of the subject in the study."	
Section 6.3	"The randomization codes will be computer generated in blocks using the AstraZeneca global randomization system (AZRand) in a way that ensures approximate balance (1:1) between the 2 treatment arms." was changed to "A blocked randomization will be generated in order to reach approximate balance (1:1) between the 2 treatment arms."	It's modified as "AZRand" is not a system.
Section 6.5.2	Add the statement: "All hyperkalaemia events that require rescue therapy will be reported as an AE."	To clarify definition of hyperkalaemia related AE.
Section 9.1	"Hypothesis tested" was changed to "Null Hypothesis tested". "The event of being a responder is independent of treatment	To be more clear.

	assignment" was changed to "No difference in probability of being a responder between the treatment groups."	
Section 9.4.1.5	"No formal statistical tests will be performed." was changed to "As appropriate, statistical tests may be performed but p value will be considered as nominal."	To allow possible statistical testing for exploratory analysis.
Appendix D	Remove the abbreviation "AZRand", "F/S", "M/T", "W/Th".	The abbreviation is no longer listed in the protocol.
Appendix E	Introduction of Guidance related to COVID-19 pandemic (Appendix E)	To provide instructions to investigators related to COVID-19.
CSP content	The wording "Hypo/Hyperkalemia" were changed to "Hypo/Hyperkalaemia".	Use UK spelling
Version 2.0, 08 January 2020		
Section	**Summary of change**	**Reason for Change**
Section 1.1 Table 1	"Confirmed with uterine ultrasound if pregnancy test result is questionable." changed to "A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one or two weeks) or a uterine ultrasound if pregnancy test result is questionable."	To be consistent with section 5.3.4 Pregnancy.
Section 1.1 Table 2	"Confirmed with uterine ultrasound if pregnancy test result is questionable." changed to "A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one	To be consistent with section 5.3.4 Pregnancy.

	or two weeks) or a uterine ultrasound if pregnancy test result is questionable."	
Section 5.2	"Participation in another clinical study with an investigational product administered in the last 1 mouth before screening" changed to "Participation in another clinical study with an investigational product administered in the last 1 month before screening"	To correct typographical error.
Section 6.2	Further guidance and information for the final disposition of unused study treatment are provided in the IP Handling Instruction changed to "Further guidance and information for the final disposition of unused study treatment are provided in the IP management plan."	To update the appropriate reference document for the guidance and information of unused study treatment.
Section 6.5	Deleted "and/or beta blocking agents"	To be consistent with DIALIZE study CSP.
Section 8.2.1	B- Erythrocyte count (RBC) was added to Haematology test (Table 8)	To align with China local clinical practice.
Section 11 – Appendix A1	New information added to describe the Regulatory Reporting Requirements for Serious Adverse Events (SAEs)	To describe the Investigator and Sponsor regulatory reporting requirements of SAEs.
Section 11 – Appendix A7	New information added to describe the process for study site closure and/or study termination	To clarify how and when individual study sites can be closed and/or terminate the study as a whole.
Version 1.0, 15 August 2019		
Initial creation		

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.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of assessments – screening

Visit	**1**	**2**	**3**	**For details see Section**
Day	**-7**	**-5**	**-3**	
Type of visit	**L**	**S**	**S**	
Informed consent	X			Appendix A2
Inclusion /exclusion criteria	X	X	X	5.1, 5.2
Demographics	X			
Medical/surgical history [a,b]	X			
Physical examination	X			8.2.2
Vital signs and BP [c]	X			8.2.3
Weight [d]	X	X	X	
Height	X			
Safety lab assessments	X			8.2.1
Serum hCG pregnancy test [e]	X			
12-lead ECG	X			8.2.4
Serum Potassium (S-K) [f]	X	X	X	8.1.1
Concomitant medication	X	X	X	6.5
Dialysate K prescription	X	X	X	8.1.2
Dialysis prescription [g]	X			8.2.5.1
Dialysis adequacy [h]	X			8.2.5.2
Post-dialysis weight after the prior dialysis session [i]	X	X	X	8.2.5.3
AE review	X	X	X	8.4

[a] Including dialysis history: (I) dialysis vintage (time since first dialysis in years); (II) type of access: AV fistula, AV graft, tunnelled central venous catheter, other (specify)

[b] Including cause of end-stage renal disease (ESRD)

[c] Vital signs and BP should be measured prior to the haemodialysis procedure. HR and BP should be measured in triplicate after being comfortably at rest in either supine or seated position quietly for at least 5 min.

[d] Dry weight and pre-dialysis weight on Visit 1; pre-dialysis weight on all other visits.

[e] Collect from female subjects of childbearing potential only. A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one or two weeks) or a uterine ultrasound if pregnancy test result is questionable.

[f] Serum Potassium sampling: pre-dialysis central laboratory (c-Lab) during screening.

[g] Blood flow (Qb, ml/min), time on dialysis (minutes), prescribed ultrafiltration rate (ml), dialysate flow (Qd, ml/hr).

[h] spKt/V and/or urea reduction ratio (URR); record the most recent value but this should be no older than 5 weeks.

[i] The prior session post-dialysis weight, measured at immediate dialysis session prior to the study visit. To be used in the calculation of Interdialytic weight gain.

L: Long inter-dialytic interval (LIDI)
S: Short inter-dialytic interval (SIDI)

Table 2 Schedule of assessments – treatment and follow-up phase

Visit description	**Randomization**																		**EOT**	**EOS**	**PSDV**	**For details see Section**
Period	**Dose-adjustment**											**Evaluation**								**FU**		
Visit	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**		
Day	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**22**	**24**	**29**	**31**	**36**	**38**	**43**	**45**	**50**	**52**	**57**	**71 +/- 3**		
Type of visit	**L**	**S**	**S**	**L**	**S**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**			
Physical examination	X			X [k]			X [k]		X [k]								X [k]			X	X	8.2.2
Vital signs and BP [a]	X			X			X		X		X		X		X		X			X	X	8.2.3
Weight [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety lab assessments	X			X			X		X								X		X	X	X	8.2.1
Serum hCG pregnancy test [c]	X										X						X		X		X	
12-lead ECG				X							X									X	X	8.2.4
Serum Potassium [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1
i-STAT K [e]	X			X			X		X		X											8.1.3
Inclusion/Exclusion criteria	X																					5.1, 5.2
Randomization	X																					4.2.2, 6.3, 7.4
Dialysate K prescription	X	X	X	X		X	X		X		X		X		X		X		X	X	X	8.1.2

Visit description	**Randomization**																		**EOT**	**EOS**	**PSDV**	**For details see Section**
Period	**Dose-adjustment**											**Evaluation**								**FU**		
Visit	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**		
Day	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**22**	**24**	**29**	**31**	**36**	**38**	**43**	**45**	**50**	**52**	**57**	**71 +/- 3**		
Type of visit	**L**	**S**	**S**	**L**	**S**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**	**S**	**L**			
Dialysis prescription [f]	X										X								X		X	8.2.5.1
Dialysis adequacy [g]											X								X		X	8.2.5.2
Post-dialysis weight after the prior dialysis session [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.5.3
Drug dispensation/ Drug accountability [i]	X [l]			X			X		X		X		X		X		X		X [m]			6.2
Dose adjustment review [j]				X			X		X													6.1.2
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.4

[a] Vital signs and blood pressure (BP) should be measured prior to the haemodialysis procedure. Heart rate (HR) and BP should be measured in triplicate after being comfortably at rest in either supine or seated position quietly for at least 5 min.

[b] Dry weight and pre-dialysis weight on Visit 4; pre-dialysis weight on all other visits.

[c] Collect from female subjects of childbearing potential only. A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one or two weeks) or a uterine ultrasound if pregnancy test result is questionable.

[d] S-K sampling: pre- and post-dialysis c-Lab is measured after LIDI throughout the study; only pre-dialysis c-Lab is measured after SIDI throughout the study on visits as indicated in the table.

[e] Pre-dialysis i-STAT is measured during dose adjustment period after LIDI on V4 and subsequent dose review visits.
[f] Blood flow (Qb, ml/min), time on dialysis (minutes), prescribed ultrafiltration rate (ml), dialysate flow (Qd, ml/hr).
[g] spKt/V and/or urea reduction ratio (URR), record the most recent value but this should be no older than 5 weeks.
[h] The prior session post-dialysis weight, measured at immediate dialysis session prior to the study visit. To be used in the calculation of Interdialytic weight gain.
[i] Dosing Schedule Card will be reviewed to assess treatment compliance and drug accountability
[j] Dose adjustment review will be done weekly during the dose adjustment period, based on the pre-dialysis i-STAT whole blood K concentration measured following the long interdialytic interval.
[k] Targeted physical examination only.
[l] Drug accountability will not be assessed on Visit 4, only dispensation will take place.
[m] No drug dispensation will take place on the EOT Visit, only drug accountability will be assessed.

L: Long inter-dialytic interval (LIDI)
S: Short inter-dialytic interval (SIDI)
EOT: End of treatment
EOS: End of study
PSDV: Premature study discontinuation visit
FU: Follow-up

1.2 Synopsis

National co-ordinating investigator: [redacted] China.

Protocol Title: A Phase 3b, Multicentre, Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Reduce Incidence of Pre-Dialysis Hyperkalaemia with Sodium Zirconium Cyclosilicate in Chinese Subjects (DIALIZE China)

Short Title: DIALIZE China

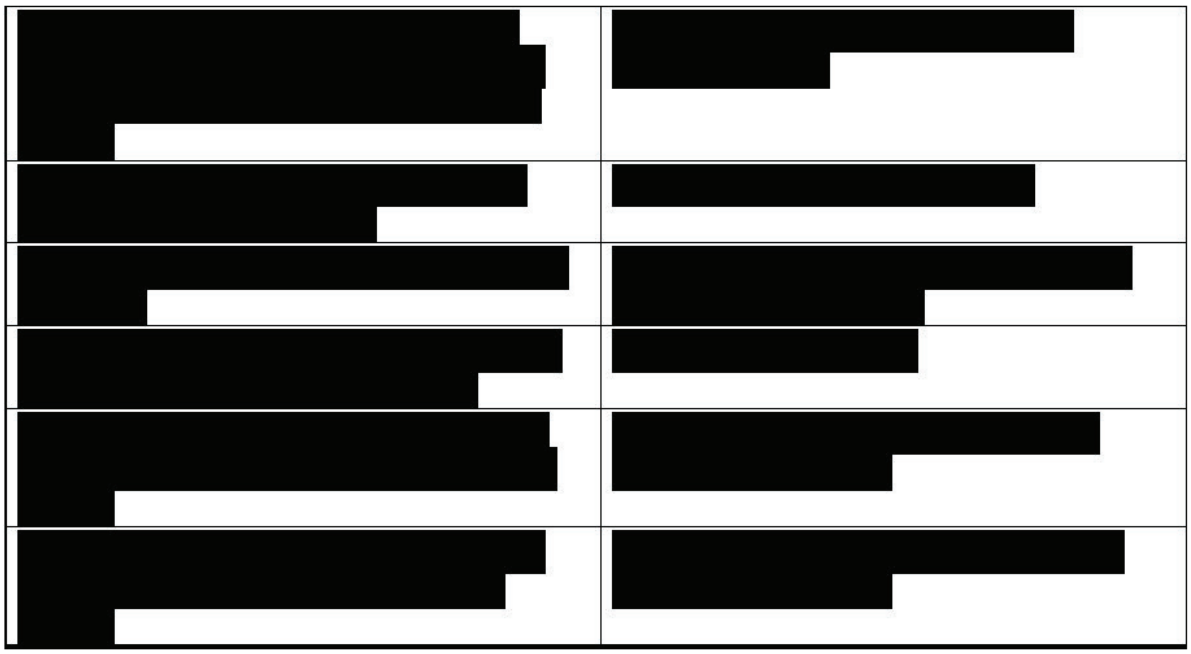
Rationale:

Recently, efficacy of Sodium Zirconium Cyclosilicate (SZC) in treatment of hyperkalaemia in subjects with end-stage renal disease (ESRD) on chronic haemodialysis was demonstrated in DIALIZE study (randomized, placebo-controlled, double-blind, Fishbane et al 2019). In the study, 41% of subjects in SZC group achieved normokalaemia on at least 3 (out of 4) long inter-dialytic interval (LIDI) visits during a 4-week long evaluation period while not receiving any rescue therapy, as compared to 1% in the Placebo group. The DIALIZE study was conducted in four countries: Japan, Russia, United Kingdom and United States. The current study has the aim of confirming efficacy and safety of SZC, as well as the appropriateness of the dosing mechanism, in Chinese ESRD subjects on chronic haemodialysis.

Study Objectives

Primary Objective:	***Endpoint/Variable:***
To evaluate the efficacy of SZC as compared to placebo in keeping the S-K concentration between 4.0 and 5.0 mmol/L in subjects on haemodialysis	Classification of each subject as either a "responder" or a "non-responder", with a responder defined as a subject who, during the evaluation period (last 4 weeks of the treatment period), maintained a pre-dialysis S-K between 4.0-5.0 mmol/L on at least 3 out of 4 dialysis treatments following the long interdialytic interval, and who do not receive rescue therapy

Secondary Objectives:	***Endpoint/Variable:***
To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis S-K concentration below 5.5 mmol/L	Pre-dialysis S-K values after SIDI and LIDI during the evaluation period
To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis LIDI S-K concentration between 5.5 and 3.5 mmol/L	Pre-dialysis S-K values after LIDI during the evaluation period
To evaluate the efficacy of SZC as compared to placebo with respect to number of pre-dialysis LIDI visits with S-K concentration between 4.0 and 5.0 mmol/L	Instances of pre-dialysis after LIDI S-K between 4.0 and 5.0 mmol/L during the evaluation period
To evaluate the efficacy of SZC as compared to placebo in reducing the potassium gradient to below 3.0 mmol/L	Instances of potassium gradient of < 3.0 mmol/L after LIDI during the evaluation period
Safety Objectives:	***Endpoint/Variable:***
To assess the safety and tolerability of SZC as compared to placebo in subjects on haemodialysis.	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory and ECG. Assessments related to AEs include: • Occurrence/Frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP
To assess the interdialytic weight gain in subjects on haemodialysis, in subjects on SZC as compared to placebo.	Interdialytic weight gain (IDWG)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



Overall design:

This is a randomized, double-blind, placebo-controlled study to determine the safety and efficacy of SZC in ESRD subjects with hyperkalaemia and on stable haemodialysis. This study consists of a screening period, an 8-week randomized treatment period, and a follow-up period. Stable haemodialysis subjects with persistent pre-dialysis hyperkalaemia will be enrolled in the study across research sites in China.

Study Period:

Estimated date of first subject enrolled Q4 2020.

Estimated date of last subject completed Q3 2021.

Number of Subjects:

Approximately 134 subjects with ESRD receiving maintenance haemodialysis treatments 3 times per week with an indication for treatment of hyperkalaemia. Subjects must have haemodialysis access consisting of an arteriovenous fistula, AV graft, or tunnelled (permanent) catheter which is expected to remain in place for the entire duration of the study.

Treatments and treatment duration:

1-week screening period, 8-week treatment period (SZC or matching Placebo), 2-week follow-up period.

Independent Data Monitoring Committee: Independent Data Monitoring Committee will be appointed for this study.

Statistical methods

[redacted]

[redacted]

[redacted]

67 subjects per group will be required to achieve an approximate power of 90%.

1.3 Schema

The general study design is summarised in Section 4.1 “Overall design”.

2 INTRODUCTION

2.1 Study rationale

Recently, efficacy of SZC in treatment of hyperkalaemia in subjects with end-stage renal disease (ESRD) was demonstrated in DIALIZE study (randomized, placebo-controlled, double-blind, Fishbane et al 2019). In the study, 41% of subjects in SZC group achieved normokalaemia on at least 3 (out of 4) long inter-dialytic interval (LIDI) visits during a 4-week long evaluation period while not receiving any rescue therapy, as compared to 1% in the Placebo group. The DIALIZE study was conducted in four countries: Japan, Russia, United Kingdom and USA. The current study has the aim of confirming efficacy and safety of SZC, as well as the appropriateness of the dosing mechanism, in the Chinese ESRD subjects on chronic haemodialysis.

2.2 Background

Hyperkalaemia is defined as an abnormally high (commonly, greater than 5.0 mmol/L) serum potassium (S-K) concentration. The incidence of hyperkalaemia is up to 10% in hospitalized subjects, and 2-3% in the general population (Kovesdy 2015). Potassium homeostasis is essential for maintaining the cellular membrane potential and proper neuromuscular functioning, with hyperkalaemia impairing neuromuscular, cardiac, and gastrointestinal function. Hyperkalaemia often presents without symptoms or with non-specific symptoms including malaise, confusion, muscle weakness or signs of cardiac arrhythmias (Henneman et al 2016). The risk of fatal cardiac arrhythmias is increased, especially at S-K concentration above 6.0 mmol/L and the mortality risk is also increased, even with modest elevations of S-K (Collins et al 2017, Nakhoul et al 2015).

The most common underlying cause of hyperkalaemia is decreased urinary potassium excretion due to reduced kidney function, as in subjects with chronic kidney disease (CKD) and heart failure (HF), or due to pharmacologic treatments, such as renin angiotensin-aldosterone inhibitors (RAASi) (Einhorn et al 2009, Fleet et al 2012, Kovesdy 2015). As the underlying causes of hyperkalaemia are often chronic conditions that worsen over time, there is a need for treatments that not only correct S-K into the normal range, but also maintain S-K within this range over longer periods of time.

The kidney plays a major role in eliminating potassium. Subjects with ESRD have reduced renal potassium excretion ability which frequently leads to hyperkalaemia. These subjects depend on the administration of renal replacement therapies (e.g. haemodialysis including low K dialysates as necessary), dietary potassium restriction, and, occasionally, the use of oral potassium binding resins to maintain serum potassium concentration in a physiologic range (Luo et al 2016, Kovesdy et al 2007). Despite dialysis, the prevalence of hyperkalaemia remains high in this population: as high as 62.9 per 100 subjects-months at the end of the long interdialytic interval (LIDI) (Yusuf et al 2016). Although potassium-binding resins are used in some instances to

treat hyperkalaemia in dialysis subjects, these agents have not been systematically studied, they are not universally used, and have no specific indications in this population.

High serum potassium can lead to ventricular arrhythmias and cardiac death. Recent studies have shown that among subjects with ESRD on haemodialysis therapy, S-K > 5.6 mmol/L is associated with increased mortality, both all-cause and cardiovascular, as compared to a referent category of S-K concentration between 4.6 to 4.99 mmol/L (Kovesdy et al 2007, Yusuf et al 2016). Importantly, sudden cardiac death (SCD) is the leading cause of death in haemodialysis subjects. In the United States Renal Data System (USRDS) database, 26.9% of all-cause mortalities in prevalent dialysis subjects between 2009 and 2011 were attributed to cardiac arrest or arrhythmias. The incidence of SCD in haemodialysis subjects was 49.2 per 1000 subjects-years in 2011, which is much higher than that of the general population (Huang et al 2015). Hyperkalaemia is also associated with greater short-term risk of hospitalization and emergency department visits, and with greater hospital costs in subjects on haemodialysis (Brunelli et al 2017). Hence prevention and treatment of hyperkalaemia in haemodialysis subjects are of paramount importance.

Sodium zirconium cyclosilicate (SZC) is a non-absorbed, inorganic crystalline compound that selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract after oral administration. Thereby, excess potassium is removed from the body through faecal excretion and serum potassium is decreased. The effect of SZC in reducing S-K was consistently demonstrated in the clinical development programme. In randomized, double-blind, placebo-controlled studies in non-dialysis subjects, SZC rapidly, effectively and safely reduced S-K into the normokalaemic range across a broad population of subjects with hyperkalaemia and with various underlying comorbidities, concomitant treatments, and demographic characteristics. Furthermore, continued SZC administration effectively maintained normokalaemia for up to 12 months. Importantly, DIALIZE study demonstrated SZC is effective in maintaining normokalaemia during LIDI in the segment of the hyperkalaemia patient population on chronic haemodialysis.

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

2.3 Benefit/risk assessment

The primary benefit for subjects randomized to SZC treatment is expected to be the maintenance of normokalaemia during the long interdialytic interval, in line with what was observed in DIALIZE study, potentially including the relief of associated signs and symptoms and an improved quality of life. The likelihood of treatment with SZC raising safety concerns is deemed to be low, as no clinically relevant safety findings were observed in DIALIZE.

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

An established dose adjustment algorithm will be used during the study to titrate investigational product (IP) doses to enable subjects to achieve and maintain pre-dialysis normokalaemia after the LIDI, while evaluating any changes in prescribed dialysate potassium concentrations. In accordance with the algorithm, the IP dose may be increased, reduced or kept unchanged, depending on the current potassium concentration, adapting the dosing regimen to each subject 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, oedema peripheral, peripheral swelling). In the study, the risk for hypokalaemia is mitigated by periodic monitoring of K and adjustment of the dose of IP as necessary. Oedema can be managed by conservative measures in line with standard clinical practice. No additional safety risks were identified in DIALIZE study.

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

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of SZC may be found in the Investigator's Brochure.

See Section 9.5.1 "Independent Data Monitoring Committee" for information regarding the Independent Data Monitoring Committee.

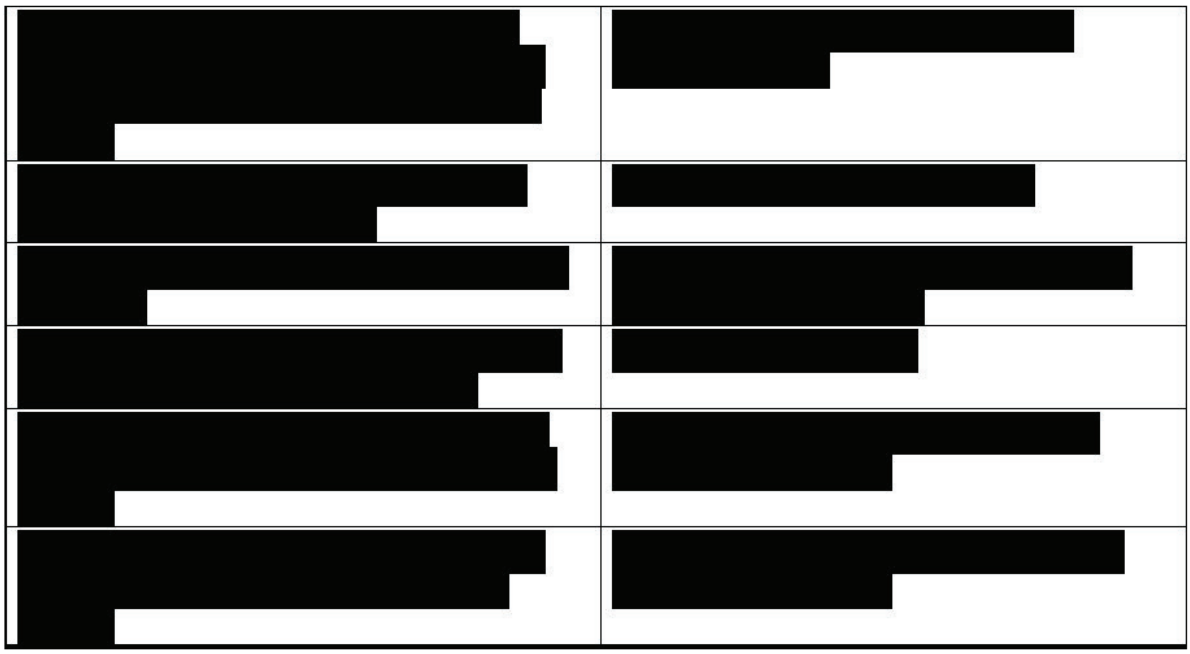
3 OBJECTIVES AND ENDPOINTS

The objectives of the study, as well as the associated endpoints, are listed in table below. For all the objectives, the analyses performed in order to address them will be reported in CSR. For a detailed discussion of these analyses, including the definition of statistical hypotheses and estimands, see Section 9 "Statistical Considerations".

Table 3 Study Objectives

Primary Objective:	***Endpoint/Variable:***
To evaluate the efficacy of SZC as compared to placebo in keeping the S-K concentration between 4.0 and 5.0 mmol/L in subjects on haemodialysis	Classification of each subject as either a "responder" or a "non-responder", with a responder defined as a subject who, during the evaluation period (last 4 weeks of the treatment period), maintained a pre-dialysis S-K between 4.0-5.0 mmol/L on at least 3 out of 4 dialysis treatments following the long interdialytic interval, and who do not receive rescue therapy

Secondary Objectives:	***Endpoint/Variable:***
To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis S-K concentration below 5.5 mmol/L	Pre-dialysis S-K values after SIDI and LIDI during the evaluation period
To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis LIDI S-K concentration between 5.5 and 3.5 mmol/L	Pre-dialysis S-K values after LIDI during the evaluation period
To evaluate the efficacy of SZC as compared to placebo with respect to number of pre-dialysis LIDI visits with S-K concentration between 4.0 and 5.0 mmol/L	Instances of pre-dialysis after LIDI S-K between 4.0 and 5.0 mmol/L during the evaluation period
To evaluate the efficacy of SZC as compared to placebo in reducing the potassium gradient to below 3.0 mmol/L	Instances of potassium gradient of < 3.0 mmol/L after LIDI during the evaluation period
Safety Objectives:	***Endpoint/Variable:***
To assess the safety and tolerability of SZC as compared to placebo in subjects on haemodialysis	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory and ECG. Assessments related to AEs include: • Occurrence/Frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP
To assess the interdialytic weight gain in subjects on haemodialysis, in subjects on SZC as compared to placebo	Interdialytic weight gain (IDWG)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

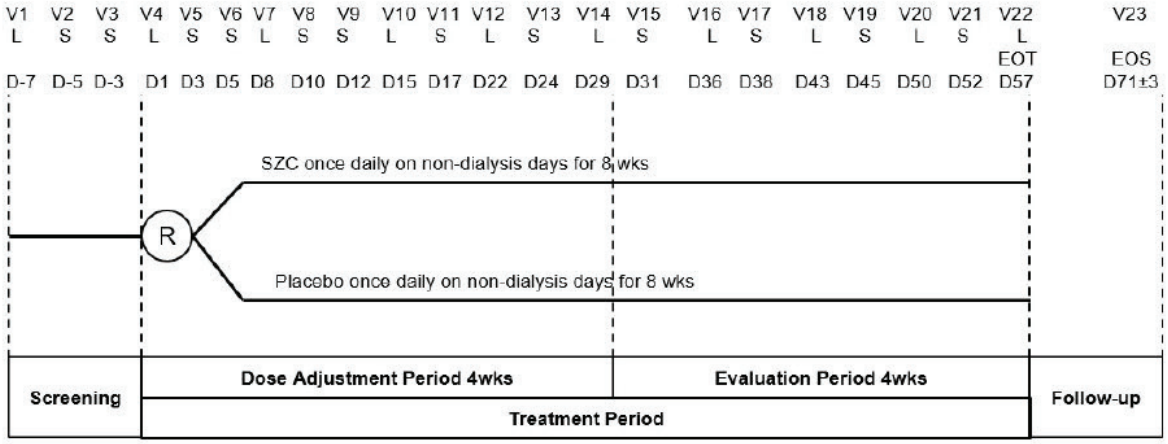


4 STUDY DESIGN

4.1 Overall design

This is a randomized, double-blind, placebo-controlled Phase 3b study to evaluate the efficacy and safety of SZC in the treatment of hyperkalaemia in Chinese subjects with ESRD on stable haemodialysis. Approximately 134 subjects with ESRD receiving maintenance haemodialysis treatments 3 times per week will be randomized in the study across research centre in China, in a 1:1 ratio, to SZC or Placebo.

Figure 1 Study design



V=Visit; D=Day; wks=weeks
L= visit following the long interdialytic interval; S= visit following the short interdialytic interval;
R=Randomization; EOT= End Of Treatment; EOS=End Of Study;

Each subject will spend approximately 11 weeks in the study and take part in at least two visits per week, with the exception of the follow-up period, on a LIDI day (long inter-dialytic interval, two consecutive days between dialyses) and at least one of the two SIDI days (short inter-dialytic interval, only one day between dialyses sessions). In the figure, the LIDI visits are marked by "L" and it is these visits that are of primarily interest in the study.

The study will consist of four study periods as follows:

Screening period, one week. This period starts on visit 1 and ends on the day prior to randomization day. At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects can be re-screened once during the clinical trial period, see Section 5.4 "Screen failures" for details.

Dose Adjustment period, four weeks. This period starts with visit 4, when randomization takes place, and ends at visit 14. During this period, the dose is titrated to achieve and maintain pre-dialysis after-LIDI S-K between 4.0 and 5.0 mmol/L. The maximum allowable IP dose is 15g. See Section 6.1 "Treatments administered" for details.

Evaluation period, four weeks. This period starts day after visit 14 and ends with visit 22 (end of treatment visit, EOT). During evaluation period the dose is held stable. This is the period that will be used for the majority of the efficacy evaluations.

Follow-up period, approximately two weeks. This is an off-treatment period that starts day after visit 22 and ends with visit 23 (end of study visit, EOS), with the primary purpose of capturing potential post-treatment safety issues.

The following visits are of special importance:

Visit 1, enrolment. This is the very first visit of the study on which the informed consent form (ICF) should be signed and first study procedure undertaken. Premature signing of ICF, i.e. signing before visit 1, should be avoided. A subject will be considered as enrolled in the study from the time the first ICF is signed (signing multiple ICFs might be necessary e.g. in case of re-screening). See Appendix

A2 "Informed consent process" for further information regarding ICF.

Visit 4, randomization. This is the visit at which the randomization code is obtained, and a subject is randomized to either SZC or Placebo, provided they have fulfilled the eligibility criteria and were not withdrawn (e.g. subject decision). For further information regarding randomization process, see Sections 4.2.2 "Methods for blinding and unblinding" 6.3 "Measures to minimise bias: randomisation and blinding" and 7.4 "Procedure for erroneously randomized subjects".

Visit 22, end of treatment (EOT). This is the last visit of the evaluation period, as well as treatment period overall. If no premature treatment discontinuation occurred, this is also the day after which no IP should be taken. For details on the process of premature treatment discontinuation see Section 7.1 "Discontinuation of study treatment".

Visit 23, end of study (EOS). This is the very last scheduled visit of the study with no assessments planned to take place after it. It should take place 14 +/- 3 days after the EOT visit to match the dialysis schedule.

Extra visit, premature study discontinuation visit (PSDV). This visit is only relevant for subjects that are withdrawn from the study (note that this differs from treatment discontinuation). It might occur at any point during the study and no information should be collected after the visit takes place. In particular, such subjects will not have an EOS visit, with the premature study discontinuation visit replacing it. For further details on the process of premature study discontinuation see Section 7.3 "Withdrawal from the study".

For an overview of the study design see Figure 1 "Study design", Section 4.1"Overall design". For details on treatments given during the study, see Section 6.1 "Treatments Administered".

For details on what is included in the efficacy and safety endpoints, see Section 3 "Objectives and Endpoints".

4.2 Scientific rationale for study design

The study is designed to provide efficacy data for the SZC clinical development program and provide information relevant to the efficacy of SZC in the treatment of hyperkalaemia in Chinese haemodialysis subjects with ESRD. The study is a randomized, double-blind study with two treatment groups, SZC or placebo, and includes haemodialysis subjects that have been on dialysis for a minimum of 3 months and receive treatment 3 times a week. No clinically justified therapy for severe acute hyperkalaemia will be withheld in study subjects. Rescue therapy will be available according to local practice patterns. Thus, placebo is deemed to be the appropriate comparator in this study.

Although it is the LIDI visits that are of primary interest for the purpose of demonstrating efficacy, scheduled SIDI visits are also included for closer safety monitoring to identify potential hypokalaemia.

The duration of the study (four weeks dose adjustment and four weeks evaluation) reflects the clinical practice monthly potassium monitoring.

4.2.1 Justification of endpoints

The primary and secondary endpoints of the study reflect the desired claim of SZC being superior to Placebo in terms of decreasing, and maintaining, S-K, as well as K gradient, within

low-risk ranges for ESRD subjects on haemodialysis. The secondary endpoints support the primary claim and capture additional aspects of S-K profiles for individual subjects.

4.2.2 Methods for blinding and unblinding

The randomized treatment phase will have a double-blind design. Subjects will take by mouth assigned dose from the sachet(s) containing either SZC or placebo. Individual sachets are enclosed in a carton with a tamper evident seal intended to be broken exclusively by subjects just before taking the study drug. The randomization will be performed using IVRS/IWRS.

In case of unblinding situation, individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

For further details, see Section 6.3 “Measures to minimise bias: randomisation and blinding”.

4.3 Justification for dose

Initial (hyperkalaemia correction) and maintenance doses of SZC were studied extensively in the Phase 2 and Phase 3 programs. The doses to be used in this study are consistent with those found to be effective for maintenance of normokalaemia in the non-dialysis population and in DIALIZE study. Dose adjustments were allowed in DIALIZE study according to pre-specified rules in order to normalize S-K concentration and minimize hypokalaemia.

For details regarding the dosing regimen, see Section 6.1 “Treatments administered”.

4.4 End of study definition

The end of study is defined as the date of the last visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study if he/she has completed visit 23, EOS, which is the last scheduled visit at which study-related measurements are obtained.

See Appendix A4 “Dissemination of clinical study data” for guidelines for the dissemination of study results.

5 STUDY POPULATION

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

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can

there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, see Section 5.4 “Screen failures” for details.

In this protocol, “enrolled” subjects are defined as those who sign informed consent. “Randomized” subjects are defined as those who undergo randomization and receive a randomization number.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix

A2 “Informed consent process”.

Age

2 Subject must be ≥ 18 years of age inclusive, at the time of signing the informed consent form.

Type of subject and disease characteristics

3 Subjects must have haemodialysis access consisting of an arteriovenous fistula, AV graft, or tunnelled (permanent) catheter which is expected to remain in place for the entire duration of the study.

4 Receiving haemodialysis (or hemodiafiltration) 3 times a week for treatment of end-stage renal disease (ESRD) for at least 3 months before randomization.

5 Pre-dialysis S-K > 5.4 mmol/L after long inter-dialytic interval and > 5.0 mmol/L after at least one short inter-dialytic interval during screening (as assessed by central lab).

6 Prescribed dialysate K concentration ≤ 3 mmol/L during screening.

7 Sustained Qb ≥ 200 ml/min and spKt/V ≥ 1.2 (or URR ≥ 63) on stable haemodialysis / haemodiafltration prescription during screening with prescription (time, dialyzer, blood flow [Qb], dialysate flow rate [Qd] and bicarbonate concentration) expected to remain unchanged during study.

8 Subjects must be receiving dietary counselling appropriate for ESRD subjects treated with haemodialysis / haemodiafiltration as per local guidelines, which includes dietary potassium restriction.

5.2 Exclusion criteria

Medical conditions

1 Myocardial infarction, acute coronary syndrome, stroke, seizure or a thrombotic / thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism, but excluding vascular access thrombosis) within 12 weeks prior to randomization.

2 Pseudohyperkalaemia secondary to haemolyzed blood specimen (this situation is not considered screening failure, sampling or full screening can be postponed to a later time as applicable).

3 Diagnosis of rhabdomyolysis during the 4 weeks preceding randomization.

4 Presence of cardiac arrhythmias or conduction defects that require immediate treatment.

5 Any medical condition, including active, clinically significant infection or liver disease, that in the opinion of the investigator or Sponsor may pose a safety risk to a subject in this study, which may confound safety or efficacy assessment and jeopardize the quality of the data, or may interfere with study participation.

6 History of QT prolongation associated with other medications that required discontinuation of that medication; congenital long QT syndrome or QTc(f) > 550 msec; uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication or with transient atrial fibrillation associated with dialysis or peridialytic period are permitted.

Prior/concomitant therapy

7 Subjects treated with sodium polystyrene sulfonate (e.g. SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) or patiromer (Veltassa) within 7 days before screening or anticipated in requiring any of these agents during the study.

Prior/concurrent clinical study experience

8 Participation in another clinical study with an investigational product administered in the last 1 month before screening.

Diagnostic assessments

9 Haemoglobin < 9 g/dL on screening (as assessed on Visit 1).

10 Laboratory diagnosis of hypokalaemia (K < 3.5 mmol/L), hypocalcemia (Ca < 8.2 mg/d or albumin-corrected Ca < 8.0 mg/dL if the latter is used in local practice), hypomagnesemia (Mg < 1.7 mg/dL) or severe acidosis (serum bicarbonate 16 mEq/L or less) in the 4 weeks preceding randomization.

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

12 Polycythaemia (Hb > 14 g/dL) during screening.

Other exclusions

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

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

15 Previous randomisation in the present study.

16 For women only - currently pregnant (confirmed with positive pregnancy test or uterine ultrasound if pregnancy test is questionable) or breast-feeding.

17 Females of childbearing potential, unless using contraception as detailed in the protocol or sexual abstinence (see Section 5.3 "Lifestyle restrictions").

18 Lack of compliance with haemodialysis prescription (both number and duration of treatments) during the two-week period preceding screening (100% compliance required).

19 Subjects unable to take investigational product drug mix.

20 Scheduled date for living donor kidney transplant.

21 Subjects with a life expectancy of less than 6 months.

22 Known hypersensitivity or previous anaphylaxis to SZC or to components thereof.

23 History of alcohol or drug abuse within 2 years prior to randomization.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

Subject will have to follow dietary counselling and be compliant with diet. Dialysis clinics included in the study should provide subjects dietary advice compiled from clinical sources and local Nephrology societies' recommendations that are consistent with the KDOQI (US) and KDIGO (global) guidelines. Subjects should be instructed on avoidance of high potassium foods as well as selection of low potassium foods in order to restrict daily dietary potassium intake to between 2 and 2.5 g or as described by local guidelines.

Although details may vary across sites (from general advice to detailed instructions), the overall approach should be to give subjects dietary advice targeted to maintain low potassium intake (limited amount of high-potassium food, restrictions on raw vegetables) while maintaining adequate nutrition in terms of protein and caloric intake. The use of print educational materials to educate subjects is encouraged.

5.3.2 Caffeine, alcohol, and tobacco

No restrictions regarding caffeine, alcohol or tobacco intake, beyond those specified by dietary counselling as described above.

5.3.3 Activity

No physical activity restrictions.

5.3.4 Pregnancy

Female subjects must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 1 month after the last dose of SZC/Placebo to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.

Sexual abstinence (true abstinence in line with the subjects preferred and usual lifestyle) is considered an acceptable method of birth control. Subjects practicing abstinence will agree to have a documented second acceptable method of birth control such as a combination of the following: (1) oral contraceptive, depo progesterone or intrauterine device; and (2) a barrier method (condom or diaphragm), should they become sexually active during the course of study participation.

Serum levels of beta HCG can be elevated in ESRD patients on dialysis in the absence of pregnancy. A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one or two weeks) or a uterine ultrasound.

5.3.5 Other

Subject should be compliant with haemodialysis prescription (both number and duration of treatments)

The following should remain unchanged during the entire study unless, in the judgment of the investigator, an unanticipated urgent clinical situation requires a change.

- Haemodialysis prescription including treatment time and frequency (3/week), dialyzer size and type, blood flow (Qb) ≥ 200 ml/min and dialysate bicarbonate concentration (dialysate potassium concentration can be modified as specified in the protocol, see Section 6.1.2 “Dose and treatment regimens” for details).

- Haemodialysis access consisting of an arteriovenous fistula, AV graft, or tunnelled (permanent) catheter.The study physician should be informed if the investigator deems

that changes in any of these parameters is necessary or if a subject is noncompliant with haemodialysis prescription.

Any changes should be recorded in the eCRF.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but did not fulfil the eligibility criteria and, as a consequence, were not subsequently randomized to a treatment group via the IVRS/IWRS. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects 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, any serious adverse event (SAE) and information necessary to link laboratory assessments with c-Lab data.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. Re-screened subjects will keep the originally assigned enrolment number. Repeated assessments will be documented as re-screening visits in the eCRF. Subjects who cannot complete the screening process due to sample issue is not considered screening failure, sampling or full screening can be postponed to a later time as applicable.

Enrolled subjects who are not randomized (this could e.g. be due to screen failure or subject decision) should have the reason for study withdrawal recorded in the eCRF.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to SZC or Placebo.

6.1 Treatments administered

6.1.1 Investigational products

Table 4 Study Treatments

	Treatment 1	*Treatment 2*
Study treatment name:	Sodium Zirconium Cyclosilicate (SZC) 5 g	Placebo
Dosage formulation:	Powder for oral suspension in a sachet	Powder for oral suspension in a sachet
Route of administration	Oral	Oral
Dosing instructions:	Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by subject and administered on non-dialysis days	Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by subject and administered on non-dialysis days
Packaging and labelling	Study treatment will be provided in sachet. Each sachet will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.	

6.1.2 Dose and treatment regimens

SZC or Placebo will be suspended in 45 ml of water and administered orally on non-dialysis days for a treatment period of eight weeks. The initial IP dose will be 5 g once daily and may be adjusted to a maximum of 15 g per non-dialysis day to maintain a pre-dialysis S-K between 4.0 and 5.0 mmol/L. Subjects on nocturnal haemodialysis should wait at least 6 hours after the end of their dialysis session to take the corresponding investigational product dose.

The adjustment will take place during the first 4 weeks of the treatment period (on visits 4, 7, 10 and 12). All dose adjustments will be based on pre-dialysis potassium (K) values measured by i-STAT (whole blood). Management of dialysis prescription will be according to local clinical pattern practices. In particular:

1) If pre-dialysis LIDI K as measured by i-STAT is > 5.0 mmol/L. For subjects taking 5 g on non-dialysis days, the dose should be increased to 10 g on non-dialysis days. For subjects taking 10 g, the dose should be increased to 15 g on non-dialysis days.
2) If pre-dialysis LIDI K as measured by i-STAT is 4.0-5.0 mmol/L. The dose should remain unchanged.

3) If pre-dialysis LIDI K as measured by i-STAT is < 4.0 mmol/L. The action to be taken depends on whether an increase in dialysate K concentration is feasible according to local practice. Explicitly:

   3a) *For sites that adopt the clinical practice of modifying the prescribed dialysate potassium concentration when the pre-dialysis potassium concentration decreases.*

   If pre-dialysis K is below 4.0 mmol/L the dialysate K concentration should be increased by 0.5 or 1 mmol/L according to standard of care, e.g. increase dialysate K from 1 K (1 K= 1 mmol/L) to 1.5 or 2 K, from 2 K to 2.5 or 3 K, or from 3 K to 3.5 or 4 K. If dialysate K concentration cannot be increased further (e.g. subject already using 4 K dialysate bath), the dose of IP can be decreased by 5 g. This will result in dose 0, i.e. no IP given, if already at 5 g.

   3b) *For sites where local clinical practice does not include increasing the dialysate K concentration when pre-dialysis potassium concentration decreases.*

   The dose of IP can be decreased by 5 g. This will result in dose 0, i.e. no IP given, if already at 5 g.

   If during the treatment phase (initial 4 weeks) the dose of IP has been reduced, and the pre-dialysis potassium value after the next long interdialytic interval is above 5.0 mmol/L, every effort should be made to increase the dose by 5 g or restart IP 5 g.

After the first 4 weeks, no additional adjustments of IP dose or dialysate potassium concentration should be made unless, in the judgement of the principal investigator (PI), there is a compelling medical need to treat an abnormal K concentration, i.e. severe hypokalaemia with clinical manifestations. If such an event were to occur, the appropriate IP dose adjustment (reduction) can be made with documentation of the event. In the case of hyperkalaemia with clinical manifestations deemed to require urgent treatment, rescue therapy can be administered, followed by proper documentation of the event. See Section 6.5.2 “Rescue medication” for definition of rescue therapy.

If at any time during the study a potassium value (i-STAT, c-Lab or local lab) measured on a non-dialysis day or pre-dialysis is < 3.0 mmol/L, study drug should be withheld and hypokalaemia should be managed as per standard practice. The patient should be evaluated for any intercurrent illness or comorbidity that may increase the risk of hypokalaemia. The study physician should be contacted to discuss further participation of the subject in the study. In addition, if the potassium value is < 2.5 mmol/L (severe hypokalaemia) the subject should be

promptly discontinued from study treatment as per Section 7.1 "Discontinuation of study treatment".

6.1.3 Medical devices

The i-STAT medical device (manufactured by Abbott®) is provided for use in this study.

Instructions for i-STAT use are provided in the i-STAT Reference Manual.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments 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. All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the IP management plan.

6.3 Measures to minimise bias: randomisation and blinding

All subjects will be centrally assigned to randomised study treatment using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

A blocked randomization will be generated in order to reach approximate balance (1:1) between the 2 treatment arms. No stratification will be employed.

If a subject withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

The randomization process should proceed as follows. The investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign the potential subject a unique enrolment number, beginning with 'E#', via IWRS/IVRS.
3. Determine subject eligibility. See Section 5.1 "Inclusion criteria" and 5.2 "Exclusion criteria"
4. Eligible subjects to be assigned unique randomization code via IWRS/IVRS system

The randomisation code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

Routines for all measures listed in Section 6.3 "Measures to minimise bias: randomisation and blinding" will be described in the IVRS/IWRS user manual that will be provided to each centre.

6.4 Treatment compliance

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF. Dosing Schedule Card will be completed by subjects to assess treatment compliance and IP accountability.

The study site staff is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the subject has returned all unused IP.

6.5 Concomitant therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplement that the subject 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

Any treatment given in violation of restrictions given in Table 5 "Restricted medications" will be classified as "disallowed" in the CSR.

Table 5 Restricted medications

Medication/class of drug:	***Usage (including limits for duration permitted and special situations in which it's allowed):***
Loop Diuretics: Bumetanide (Bumex), Ethacrynic acid (Edecrin), Furosemide (Lasix), Torsemide (Demadex)	Changes to loop diuretics (including adding a new, changing the dose or discontinuation or switching of loop diuretics) during the study are discouraged. If changes in loop diuretics are clinically indicated, this should be documented in the eCRF.

Any prohibited treatment present in Table 6 "Prohibited medications" will be classified as "disallowed" in the CSR.

Table 6 Prohibited medications

Prohibited medication/class of drug:	
Sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) or patiromer (Veltassa)	These drugs should be avoided during the study and can only be used as rescue 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, the IP should be administered at least 2 hours before or 2 hours after oral medications with gastric pH dependent bioavailability to mitigate the risk of drug interactions.

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

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

Table 7 Drug interactions

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

Changes to RAAS inhibitor (including adding a new, changing the dose or discontinuation or switching of RAAS inhibitor) during the study are discouraged. Similarly discouraged are changes to traditional Chinese medicine (including adding a new, changing the ingredient

content or frequency or discontinuation of traditional Chinese medicine decoction). Should such a change be required, the instance should be recorded in the eCRF.

6.5.1 Other concomitant treatment

Other medication than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

6.5.2 Rescue medication

Rescue medication will be provided by the site or the institute where the subject is treated with rescue medication.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded.

Rescue therapy can be one of the following:

1) A treatment belonging to potassium binders: sodium polystyrene sulfonate (e.g. SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (e.g. CPS, Resonium calcium) and patiromer (e.g. Veltassa). It could also be a beta-adrenergic agonist, sodium bicarbonate, insulin/glucose.
2) Any additional dialysis or other forms of renal replacement treatments when used specifically for the treatment of severe hyperkalaemia.
3) Any reduction in the dialysate K concentration that is prescribed for the treatment of severe hyperkalaemia during the study is also considered rescue therapy.

Rescue therapy should be guided by local clinical practice patterns and preferably limited to the setting of severe hyperkalaemia (>6 mmol/L). Rescue therapy should be followed by the appropriate dose adjustment if appropriate and proper documentation of the event.

All hyperkalaemia events that require rescue therapy will be reported as an AE.

6.6 Dose modification

As outlined in Section 6.1.2 "Dose and treatment regimens" the IP dose will be titrated from 5 g to 0, 5, 10 or 15 g depending on current potassium value as measured by i-STAT. As indicated in the same section, dose can also be modified during the evaluation period in presence of a compelling medical need to treat an abnormal potassium concentration. No other dose modifications should be performed.

6.7 Treatment after the end of the study

Not applicable.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

At any time, subjects are free to discontinue investigational product or withdraw from the study, without prejudice to further treatment.

7.1 Discontinuation of study treatment

Subjects may be discontinued from IP in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Incorrectly randomized subject in whom the inclusion/exclusion criteria violation would put the subject at undue risk
- Adverse Event for which the investigator judges continued treatment may put the subject at undue risk
- Severe non-compliance with the Clinical Study Protocol
- Pregnancy
- Renal transplant
- Development of any study specific criteria for discontinuation, namely:
  1. Severe hypokalaemia - if severe hypokalaemia (defined by potassium values < 2.5 mmol/l on any test) occurs at any time on non-dialysis days or pre-dialysis the subject should receive appropriate medical intervention and be promptly discontinued from the study treatment. Post-dialysis hypokalaemia should be managed as per established dialysis clinic protocols and local practices. Subjects considered for discontinuation from study treatment due to post-dialysis hypokalaemia should be discussed with the study physician
  2. QT prolongation - if an absolute QTc > 550 msec, or an increase in QTc interval > 60 msec from baseline to more than 500 msec is reached the subject should immediately receive appropriate medical intervention and be discontinued from the study treatment. The QTc(f) algorithm is recommended. All subjects meeting the QTc > 500 msec criterion should immediately have potassium assessed by i-STAT and central lab, if not already done within 1 hour of the collection of the ECG.

7.1.1 Temporary discontinuation

Subjects are allowed to resume treatment if treatment has been temporarily stopped.

7.1.2 Procedures for discontinuation of study treatment

The investigator should instruct the subject to contact the site before or at the time if study treatment is stopped. A subject that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment

should be documented in the eCRF, as well as the date of treatment discontinuation. In addition, a safety evaluation including physical examination, collection of safety lab samples (including pregnancy testing), as well as vital signs, ECG and IDWG data, should be performed at the earliest possible dialysis visit after last dose of IP.

All study treatment should be returned by the subject at their next planned or unscheduled on-site study visit. Subjects permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of study treatment, for any reason, does not impact on the subject´s participation in the study. The subject should, if possible, continue attending subsequent study visits and data collection should continue according to the study protocol. If, upon discontinuation of treatment, the subject choses to withdraw from study entirely, procedures described in Section 7.3 "Withdrawal from the study" should be followed.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site. In such cases, every attempt to contact the subjects, or their next of kin, should be made. Should the subject be unreachable at the end of the study, they should be considered to be lost to follow up.

7.3 Withdrawal from the study

A subject may withdraw from the study (withdraw consent) at any time (investigational product and assessments) at his/her own request, without prejudice to further treatment.

If the subject 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 subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up subjects as medically indicated.

A subject who chooses to withdraw from the study should be asked to return for PSDV, premature study-discontinue visit, which should then take place at earliest possible dialysis visit. If the subject agrees, assessments as indicated in SoA (Section 1.1 "Schedule of Activities", Table 2 "Schedule of assessments- treatment and follow-up phase") should be performed. All study treatment should be returned by the subject. Withdrawal of consent from the study must be ascertained and documented by the investigator and recorded in the appropriate electronic Case Report Form (eCRF). If a subject withdraws from participation in the study, then his/her enrolment and randomisation code cannot be reused. Withdrawn subjects will not be replaced.

7.4 Procedure for erroneously randomized subjects

A situation might arise where, despite every effort, a subject is randomized into the study while not fulfilling one or several of the inclusion / exclusion criteria. In this case, the following steps should be undertaken:

1) Study physician should be contacted for an assessment of whether IP could pose a risk to the subject in light of the new information.
2) If yes, the subject should be discontinued from treatment (not to be confused with study discontinuation).
3) The occurrence should be documented as appropriate.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.1 "Schedule of Activities").

The investigator will ensure that data are recorded on the electronic Case Report Forms (eCRF). The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. Serum potassium concentrations, as well as safety laboratory data, will be provided in form of third-party data by central laboratory (Covance) and reconciliated with the information obtained through the eCRF.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded in the eCRF, and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of completed eCRFs will be archived at the study site after data base lock.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the ICF may be utilised for screening or baseline purposes, provided the procedures met the protocol-specified criteria.

8.1 Efficacy assessments

8.1.1 Serum potassium measurements

S-K concentrations will be measured using central laboratory (c-Lab).

Blood samples for determination of potassium will be taken at the times indicated in the SoA (see Table 1 "Schedule of assessments-screening" and Table 2 "Schedule of assessments-treatment and follow-up phase"). Serum samples will be prepared and shipped to the Central Laboratory. Results obtained from Central Laboratory will be used for statistical analyses of the study. All serum samples should be examined and any haemolyzed samples MUST be re-drawn. In the event that haemolysis or other artefacts are suspected based on the reported i-STAT result (see Section 8.1.3 "Other assessments") the sample may be re-drawn to confirm the result. Only the confirmatory sample result needs to be reported in the eCRF.

8.1.2 Dialysate potassium concentration prescription

The dialysate K concentration is used in obtaining K gradient, which is one of the secondary endpoints. See Section 9.4.1.3 "Secondary endpoint: Gradient" for definition of K gradient. See Section 6.1.2 "Dose and treatment regimens" for guidance on alteration of Dialysate K concentration prescription.

8.1.3 Other assessments

8.1.3.1 i-STAT potassium

Whole blood Potassium will be measured by i-STAT during the dose-adjustment period. The primary purpose for these measurements is to advice the investigators on whether the dose (alternatively, dialysate K concentration) should be adjusted or kept stable. Potassium values obtained from i-STAT will not be used in the analysis of efficacy, with possible exception of a sensitivity analysis aimed at evaluating the impact of missing c-Lab potassium values.

8.2 Safety assessments

Safety will be assessed throughout the study. During the course of the study, vital signs, physical examinations and laboratory tests will be performed at regular intervals.

Planned time points for all safety assessments are provided in the SoA (Section 1.1 "Schedule of Activities").

8.2.1 Laboratory safety assessments

See Table 8 "Laboratory Safety Variables" for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA. All safety laboratory measurements should be obtained pre-dialysis.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator when associated with an adverse event. The date and time of collection will be recorded as appropriate in the eCRF.

The clinical chemistry and haematology will be performed at a central laboratory contracted by AstraZeneca. Sites will be provided with ready-to-use laboratory kits, as well as appropriate instructions/manuals. Procedures for collection, processing and sending samples to the central laboratory will be provided in above-mentioned manuals.

The following laboratory variables will be measured:

Table 8 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Erythrocyte count (RBC)	S-Creatinine
B-Haemoglobin (Hb)	
B-Leukocyte count	S-Bilirubin, total
B-Leukocyte differential count (absolute count and %)	S-Alkaline phosphatise (ALP)
B-Platelet count	S-Aspartate transaminase (AST)
	S-Alanine transaminase (ALT)
	S-Gamma-glutamyl transferase (GGT)
	S-Albumin
	S-Potassium
	S-Calcium, total
	S-Sodium
	S-Chloride
	S-Creatine kinase (CK)
	S-Bicarbonate
	S-Phosphorus
	S-Glucose
	S-Blood urea nitrogen
	S-Magnesium
	S-Lactate dehydrogenase
	S-Total protein
	S Pregnancy test (serum hCG)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7 "Adverse events based on examinations and tests".

8.2.2 Physical examinations

A physical examination will be performed as specified in SoA (Section 1.1 "Schedule of Activities").

A complete physical examination includes the following: general appearance, skin, height (Day -7 only) and weight, head and neck ((including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), respiratory, cardiovascular including assessment of signs of heart failure, abdomen, and neurological systems.

The targeted physical examination includes the following: weight (weighed on the same scale in the same state of dress), skin, extremities, respiratory, cardiovascular including assessment of signs of heart failure, and abdomen.

A complete physical examination should be performed on Day -7, Day 1 and Day 71, and targeted physical examination will be conducted as specified in the SoA. Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 "Adverse events based on examinations and tests" for details. The results of the physical exam will not be registered in the eCRF, unless an AE is identified. In that case, the appropriate AE pages should be filled in.

8.2.3 Vital signs

Vital signs will be assessed at visits as specified in SoA (Section 1.1 "Schedule of Activities"). Any clinically significant changes in vital signs should be investigated and reported as AEs (see Section 8.3.7 "Adverse events based on examinations and tests").

Heart rate and blood pressure will be measured in triplicate after the subject has been comfortably at rest in either supine or seated position for at least 5 minutes. The position of the subject should be comfortable with the arm where the blood pressure is recorded to be within the level of heart (the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). The subject will be instructed to relax as much as possible and to not talk during the measurement procedure. Preferably measurement will be done with an electronic automated oscillometric device. The same device should preferably be used for the subject during the course of the study and in the same arm. Blood pressure will be measured in triplicate

with at least one-minute intervals between measurements. All the three readings will be reported in the eCRF.

The heart rate will be assessed by pulse palpation of radial artery for 30's immediately after each recording of the blood pressure. It could be also performed with an oscillometric device if this is used for blood pressure measurement. The triplicate heart rate assessments will be recorded in the eCRF.

8.2.4 Electrocardiograms

Standard 12-lead ECG will be performed as safety measurement pre-dialysis at timepoints as per SoA (Section 1.1 "Schedule of Activities"). ECG will be assessed by Investigators according to local practice.

A single ECG will be taken after the subject has been resting in the supine position for 5 minutes. The following ECG measurements will be obtained: P, PR, QRS, QT, and QTc(f) intervals. Refer to Section 7 "Discontinuation of treatment and subject withdrawal" for QTc(f) withdrawal criteria and any additional QTc(f) readings that may be necessary.

Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the investigator should determine if it is clinically significant. Clinically significant abnormalities should be reported as an AE.

Only the visit, ECG date and time, heart rate (HR), P and QRS durations, PR, QT and QTc(f) intervals, overall interpretation and relevant comments will be recorded in the eCRF. ECG recordings will be kept as source documents.

8.2.5 Other safety assessments

In addition, the following safety assessments below will be made.

8.2.5.1 Dialysis prescription

Dialysis prescription parameters including blood flow (Qb, ml/min), time on dialysis (minutes), prescribed ultrafiltration rate (ml) and dialysate flow (Qd, ml/hr) should be recorded at the times specified in Table 1 "Schedule of assessments-screening" and Table 2 "Schedule of assessments-treatment and follow-up phase".

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 "Schedule of assessments-screening" and Table 2 "Schedule of assessments-treatment and follow-up phase". 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

Interdialytic weight gain (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, see SoA) in kilograms. The calculation will be performed as part of the analysis.

8.3 Collection of 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 event definitions and additional safety information".

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3 "Follow-up of AEs and SAEs".

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from randomisation throughout the treatment period and the follow-up period, up to end of study or premature study discontinuation visit.

SAEs will be recorded from the time of signing of informed consent form until end of study or premature study discontinuation visit.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 8.4.1 "Reporting of serious adverse events". The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit

and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 8.4.1 "Reporting of serious adverse events".

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any AEs that are unresolved at the subject's last AE assessment 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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity (mild, moderate or severe)
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused subject's withdrawal from the study (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- 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
- Description of AE

It is important to distinguish between serious and severe AEs. 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 need not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but could be an SAE. Criteria for SAE can be found in Appendix B "Adverse event definitions and additional safety information".

8.3.5 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, 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 will 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 "Adverse event definitions and additional safety information" to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject 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 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.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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 (e.g., 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).

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.

8.4 Safety reporting and medical management

8.4.1 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, then Investigators or other site personnel should inform the appropriate AstraZeneca representatives within one day i.e., 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 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site staff reports a 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 B2 “Definitions of serious adverse event”.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca, unless the pregnancy is discovered before the study subject has received any study drug.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1day i.e., 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 SAEs (see Section 8.4.1 “Reporting of serious adverse events”) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.3 Overdose

For this study, any dose of IP in excess of what is specified in the protocol will be considered an overdose.

- 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 of an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel should inform appropriate AstraZeneca representatives immediately, or **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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.4.1 "Reporting of serious adverse events". For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

For the purposes of reporting in this clinical study, 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 subject or has the potential to cause harm to the subject. If a medication error occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative should work 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 8.3.2 "Time period and frequency for collecting AE and SAE information") and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B8 "Medication error".

8.4.5 Management of IP-related toxicities

See Section 6.1.2 "Dose and treatment regimens" for details on dose / dialysate K adjustment related to hypokalaemia. See Section 7.1 "Discontinuation of study treatment" for hypokalaemia-based discontinuation criteria.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

For all statistical tests, the null hypothesis will be that of no difference between treatment groups, with a two-sided alternative. The individual hypotheses will be tested using 0.05 Type I error rate and a multiplicity correction procedure will be applied (see Section 9.4.4 "Methods for multiplicity control" for details). Specifically:

Objective	***Null Hypothesis tested***
Primary	
To evaluate the efficacy of SZC as compared to placebo in keeping the S-K concentration between 4.0 and 5.0 mmol/L in subjects on haemodialysis	No difference in probability of being a responder between the treatment groups
Secondary	
To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis S-K concentration below 5.5 mmol/L	No difference in probability of the maximum S-K value during the evaluation period (LIDI and SIDI) being smaller or equal to 5.5 mmol/L between the treatment groups
To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis LIDI S-K concentration between 5.5 and 3.5 mmol/L	No difference in probability of S-K values during the evaluation period (LIDI visits) being greater or equal to 3.5 and smaller or equal to 5.5 mmol/L between the treatment groups
To evaluate the efficacy of SZC as compared to placebo with respect to number of pre-dialysis LIDI visits with S-K concentration between 4.0 and 5.0 mmol/L	No difference in expected number pre-dialysis post-LIDI S-K concentration between 4.0 and 5.0 mmol/L during the evaluation period between the treatment groups
To evaluate the efficacy of SZC as compared to placebo in reducing the potassium gradient to below 3.0 mmol/L	No difference in probability of a potassium gradient of < 3.0 mmol/L after a LIDI during the evaluation period between the two treatment groups

9.2 Sample size determination

[redacted]

[redacted]

9.3 Populations for analyses

For the purpose of the analysis, the following populations are defined:

Population	***Description***
Enrolled	All subjects who sign the ICF.
Full analysis set (FAS)	All randomized subjects.
Safety analysis set (SAS)	All subjects included in FAS who take at least one dose of IP and for whom any post-dose data are available.

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until the database is locked and Clinical Study Protocol deviations identified and properly documented.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 Efficacy analyses

All efficacy analyses will be performed using FAS. The subjects will be analysed using the treatment group they have been randomized to.

9.4.1.1 Primary endpoint

The analysis of the primary (and the secondary) endpoints will be conducted according to the intention to treat principle using FAS. Thus, the population under study consists of all subjects that are deemed as suitable for randomization by the investigators.

As stated above, the primary endpoint is a classification of each randomized subject into a responder or a non-responder category (i.e. a 0-1 type of response), with a subject being a responder if they:

a. Have pre-dialysis S-K between 4.0 and 5.0 mmol/L on at least 3 out of 4 LIDI visits that occur during the evaluation period
b. Do not receive any rescue therapy during the evaluation period

Note that this implies that, if a subject has 2 or more missing S-K values during the evaluation period, they will be classified as a non-responder.

One intercurrent event of concern has been identified in this setting, namely the use of rescue therapy. For the primary analysis, rescue therapy use is included as part of a composite endpoint, hence the addition of b) in the primary endpoint definition (this is referred to as a "Composite strategy" in ICH E9 (R1) 2017 p. 17).

The primary endpoint will be analysed using Fisher's exact test applied to the contingency table of counts of responders and non-responders in a particular treatment group with the rejection / non-rejection of the null hypothesis based on the resulting p-value. For illustrative purposes, proportions of responders in the respective treatment groups, as well as the difference in proportions with the corresponding CI, will be presented.

The primary analysis will be repeated for selected pre-specified sub-groups in order to examine the consistency of the observed effect. The list of sub-groups will be provided in SAP.

9.4.1.2 Secondary endpoint: S-K below 5.5 mmol/L and S-K between 3.5 and 5.5 mmol/L

In the analyses of these endpoints the individual S-K measurements obtained during the evaluation period will be used (at the planned LIDI and, for analysis of S-K below 5.5 mmol/L, SIDI visits). Unlike the primary endpoint, the intercurrent event will not be managed through construction of a composite. Instead, the S-K measurements obtained while a subject was receiving rescue therapy will be excluded from the analysis, reflecting a hypothetical scenario where rescue therapy is not available to subjects (i.e. a "hypothetical strategy" type of approach, see ICH E9 (R1) 2017 p. 18).

In what follows, the analysis of S-K below 5.5 mmol/L is described. The analysis of S-K between 3.5 and 5.5 mmol/L will be conducted in the same manner.

The probability that the maximum S-K value is less than or equal to 5.5 (or between 3.5 and 5.5), denoted by p, during the evaluation period for a particular subject is of interest. In order to mitigate the possible impact of missing values, this probability will be estimated by fitting a multivariate normal distribution to the S-K values in each treatment arm and defining $p = F(5.5, \ldots, 5.5)$, with F indicating the fitted cumulative distribution function (cdf). The variance of this estimator can be approximated using bootstrap. The p-value from a test of no difference between treatment groups, estimates of probabilities in each treatment group and the difference between

the two with the corresponding CI (constructed using normal approximation, if appropriate), will be presented.

9.4.1.3 Secondary endpoint: Gradient

The endpoint in this analysis are the 0-1 indicators of whether potassium gradient, defined as the difference between pre-dialysis S-K and dialysate K concentration, is below 3.0 mmol/L for each LIDI visit in the evaluation period. That is, similarly to the first secondary endpoint, multiple measurements for each subject will be considered. Again, similarly to the first secondary endpoint, the intercurrent event of rescue therapy will be incorporated through omission of observations that coincide with rescue therapy use from the analysis, resulting in the hypothetical scenario of no rescue therapy being available.

For this objective, the probability that the potassium gradient for a particular LIDI visit is below 3.0 mmol/L is of interest. This probability can be estimated for each treatment group though application of a generalized linear mixed model with random intercept and logit link. The p-value from a test of no difference between treatment groups, estimates of probability of observing a gradient below 3.0 mmol/L in each treatment group and the difference between the two groups with the corresponding CI, will be presented. The presented p-value will be obtained from the test of equality of odds ratios using the aforementioned generalized linear mixed model.

9.4.1.4 Secondary endpoint: Number of normokalaemic instances

The endpoint in this analysis are the 0-1 indicators of whether S-K is between 4.0 and 5.0 mmol/L for each LIDI visit in the evaluation period. The intercurrent event of rescue therapy will, again, be incorporated through omission of observations that coincide with rescue therapy use from the analysis.

This endpoint will be analysed through application of a generalized linear mixed model with random intercept. P-value of a test of no difference, estimates of the expected number of normokalaemic instances in the respective treatment groups, the difference between the two groups and the corresponding CI will be presented. The presented p-value will be obtained from the test of equality of odds ratios using the generalized linear mixed model.

Note that the rejection of this null hypothesis implies the rejection of the null hypothesis of no difference between the expected number of visits with S-K between 4.0 and 5.0 mmol/L, as equivalence of odds ratios implies equivalence of probabilities (of S-K between 4.0 and 5.0 mmol/L in the respective treatment groups at a particular visit) which, in turn, implies equivalence of expected number of normokalaemic visits. Similar logic applies to the test of secondary endpoint described in the previous section.

9.4.1.5 Exploratory endpoints

[redacted]

9.4.2 Safety analyses

All safety analyses will be performed using the Safety analysis set. The subjects will be analysed using the actual treatment they have been taking during the study. If a subject takes several treatments during the study, they will be analysed using the treatment they have been randomized to.

The analyses will include a tabulation of AEs, SAEs and DAEs (per SOC and/or PT, intensity, causality) in the respective treatment group, a tabulation of safety laboratory evaluations as listed in Section 8.2.1 "Laboratory safety assessments" (summary statistics such as mean, standard deviation, median, minimum and maximum), a tabulation of vital signs and ECG (similar to the one employed for safety laboratory measurements) and a tabulation of IDWG. Listings of AEs, with detailed information such as day of AE occurrence and outcome of AE, will also be provided.

9.4.3 Other analyses

Other analyses will include a tabulation of baseline demography and subject characteristics, medical history including dialysis history, compliance and exposure.

9.4.4 Methods for multiplicity control

In case of rejection of the null hypothesis corresponding to the primary endpoint, the four secondary efficacy hypotheses will be considered. A multiplicity testing procedure that controls the family-wise Type I error rate will be applied, and statistical significance will be claimed in case of rejection at the family-wise significance level of 0.05. The multiplicity testing procedure will be a fixed sequence procedure, with the hypotheses ordered as in Table 3 "Study Objectives".

9.5 Interim analyses

No interim analyses are planned for the study.

9.5.1 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will be utilized for this study.

The IDMC will be the external advisory group for the study which, on a regular basis, reviews accumulating study efficacy and safety data, to determine whether the overall integrity and

conduct of the study remain acceptable, and makes recommendations to the Sponsor. The IDMC will function independently of all other individuals associated with the conduct of the studies, including AstraZeneca. The committee will operate in accordance with an Independent Data Monitoring Committee Charter.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A1 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 Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A2 Informed consent process

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

Subjects must be informed that their participation is voluntary. Subjects 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 centre.

The medical record must include a statement that written informed consent was obtained before the subject 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.

Subjects 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 subject or the subject's legally authorised representative.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 60 days from the previous ICF signature date.

A3 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject 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 must also be explained to the subject.

The subject 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.

A4 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical trial 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.

A5 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or 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.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

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 subjects 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.

A6 Source documents

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

Data reported on 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.

A7 Study and Site Closure

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. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests

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

A8 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 event definitions and additional safety information

B1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject 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 (e.g. 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 treatment has been administered.

B2 Definitions of serious adverse event

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

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

Adverse Events (AEs) for **malignant tumours** 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 fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor 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 hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

B3 Life threatening

'Life-threatening' means that the subject 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 subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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 subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B5 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 jeopardize the subject or may require medical treatment to prevent one 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 iv 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B6 Intensity and scale

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 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 B2 "Definitions of serious adverse event". 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 a SAE unless it meets the criteria shown in Appendix B2 "Definitions of serious adverse event" On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B2 "Definitions of serious adverse event".

B7 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 subject 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 recognized 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 limited or insufficient information in the case, it is likely that 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.

B8 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 drug 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 recognize that could have led to an error

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. 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 standard of care medication in open label studies, even if an AZ product

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

Appendix C Handling of Human Biological Samples

C1 Chain of custody for biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

C2 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories
(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
ALP	Alkaline Phosphatise
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BP	Blood Pressure
CDF	Cumulative Distribution Function
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CKD	Chronic Kidney Disease
c-Lab	Central Laboratory
CONSORT	Consolidated Standards of Reporting Trials
CPS	Calcium Polystyrene Sulfonate
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
EC	Ethics Committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GMP	Good Manufacturing Practice
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IATA	International Airline Transportation Association
ICF	Informed Consent Form

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDWG	Interdialytic Weight Gain
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LIDI	Long Inter-dialytic Interval
LIMS	Laboratory information management system
LSLV	Last subject last visit
PI	Principal Investigator
PSDV	Premature Study Discontinuation Visit
PTDV	Premature Treatment Discontinuation Visit
Qb	Blood Flow (dialysis)
Qd	Dialysate Flow Rate
RAASi	Renin Angiotensin-aldosterone Inhibitors
S-K	Serum Potassium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sudden Cardiac Death
SIDI	Short Inter-dialytic Interval
SoA	Schedule of Activities
SPS	Sodium Polystyrene Sulfonate
SZC	Sodium Zirconium Cyclosilicate
URR	Urea Reduction Ratio
USRDS	United States Renal Data System
WBDC	Web Based Data Capture

Appendix E Guidance related to COVID-19 pandemic

E1 Management of Study Procedures During the COVID-19 Pandemic

In view of the ongoing and emerging novel coronavirus (COVID-19) pandemic spreading worldwide, the safety and well-being of our study participants is of primary importance. To protect the safety and well-being of study participants, this section will provide guidelines on study assessments and procedures during this period.

1. SZC is a potassium binder acting in the gastrointestinal tract and is not absorbed. No additional risk from COVID-19 is expected due to SZC. Every effort should be made to follow the clinical study protocol (CSP). Participant safety is paramount, and the investigator should continue to reassess the risk/benefit of continued study involvement for each study participant.

2. Investigational study sites must comply with local public health rules.

3. If a study participant is suspected or diagnosed with COVID-19, they should follow the local guidance for COVID19 diagnosis, quarantine, and treatment procedures.

    a) Please accurately document all diagnoses, procedures, assessments, dosing interruptions, and sequelae in the eCRFs. All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP.
    b) If a COVID-19 AE/SAE is reported, the investigator should determine whether the participant's investigational product should continue, be interrupted, or stopped in accordance with the CSP.

4. If a study participant is unable to attend clinic visits either due to quarantine for being infected with or suspected for COVID-19 or due to site closure for COVID-19, the investigational product should be discontinued, and every effort should be made to conduct safety assessment (e.g., potassium value and ECG measurement), this could be done at an alternative healthcare facility or by home visit if possible. Local lab results will not be collected or stored in the study database but will help the investigator to assess patient safety. The site staff should keep in close contact with the study participant(s), preferably through telephone calls, to maintain awareness of their status.

E2 Guidance on Covid-19 vaccination in clinical studies of SZC

Covid-19 vaccination of subjects participating in clinical studies of SZC should follow national/local guidelines. SZC is a locally acting drug in the GI tract with no systemic toxicity, immunogenic effects or a potential to interfere with the biological action of drugs affecting the immune system, including Covid-19 vaccines. An approved Covid-19 vaccine is therefore treated like any allowed medication in clinical studies with SZC.

- Vaccination prior to or during a clinical study of SZC does not limit enrolment or continued participation in the study.
- Vaccine use should be recorded in the eCRF:
  - The specific vaccine used (brand name) and each dose administered after enrolment should be recorded as concomitant medication.
  - Vaccination taking place before enrolment should be captured under "medical history".
  - Adverse events suspected of being related to vaccinations should be reported as for any other AEs.
- In accordance with general rules for AstraZeneca clinical studies, a subject participating in any other clinical study with an investigational product administered within a month before the screening, e.g. clinical study of a vaccine, is not eligible to participate in a clinical study of SZC.

The guidance above only applies to vaccines approved by health authorities including Emergency Use Authorisation by the FDA or similar authorisation by other Regulatory Agencies. Vaccines which are still in development, i.e. not yet approved, are not permitted.

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