Clinical Study Protocol	
Study Intervention	Sodium Zirconium Cyclosilicate (SZC)
Study Code	D9480C00022
Version	6.0
Date	3 March 2022

A Double-blind Randomized Placebo-controlled Parallel Design Multicenter Phase IIIb Study of the Effect of Sodium Zirconium Cyclosilicate (SZC) on Serum Potassium and Serum Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease (NEUTRALIZE)

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

Protocol Number: D9480C00022
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Study Intervention: sodium zirconium cyclosilicate (SZC)
Study Phase: IIIb
Short Title: NEUTRALIZE

Study physician name and contact information will be provided separately.

Principal investigator: PPD

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Amendment, CSP version 6.0	3 March 2022
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Amendment 6.0, 3 March 2022

Section # and Name	Description of Change	Brief Rationale
Section 5.1	Inclusion criteria 3 - Inclusion criteria number 3 had a typographical error. The range of POCT bicarbonate inclusion criteria is not changed, in line with protocol revision history for version 5.0 but has a typographical error. The correct wording should be "POCT K+ level >5 mmol/L to ≤5.9 mmol/L and POCT bicarbonate levels between 16-20 mmol/L inclusive prior to the first SZC dose on study Day 1.	Correcting typographical error

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Double-blind Randomized Placebo-controlled Parallel Design Multicenter Phase IIIb Study of the Effect of Sodium Zirconium Cyclosilicate (SZC) on Serum Potassium and Serum Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease

Short Title: NEUTRALIZE

Rationale: A double-blind randomized study that demonstrates SZC's ability to treat hyperkalemia and increase serum bicarbonate in this patient population would confirm the benefit of treating these patients with SZC and differentiate SZC from other potassium (K^+) binders. Measuring change in urine ammonium will further elucidate the mechanism behind the increase in serum bicarbonate seen with SZC. This study aims to investigate if SZC can increase serum bicarbonate in a clinically meaningful way, thus providing an option for patients who have hyperkalemia and metabolic acidosis associated with chronic kidney disease (CKD).

Objectives and Endpoints

Objectives	Endpoints	Hypotheses
Primary		
• To evaluate the efficacy of SZC as compared to placebo in maintaining normal sK+ in patients with hyperkalemia and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT without need for rescue treatment for hyperkalemia at any point during the randomized phase	• Null: No difference in the occurrence of patients having a normal sK+ on Day 29 without need for rescue treatment for hyperkalemia at any point during the randomized phase between SZC and placebo
Secondary		
• To evaluate the efficacy of SZC as compared to placebo in increasing serum bicarbonate in patients with hyperkalemia and metabolic acidosis associated with CKD	• Mean change in serum bicarbonate at Day 29 compared to baseline (Day 1) • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to EOT (Day 29) without need for rescue treatment for metabolic acidosis (low bicarbonate)	• Null: No difference in mean change in serum bicarbonate from baseline (Day 1) to Day 29 between SZC and placebo • Null: No difference in the occurrence of patients having an increase in serum bicarbonate of ≥2 mmol/L or ≥3 mmol/L from baseline (Day 1) to Day 29 without need for rescue treatment for metabolic

Objectives	Endpoints	Hypotheses
	• Occurrence (yes/no) of patients having bicarbonate ≥22 mmol/L • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥2 mmol/L from baseline (Day 1) to EOT without need for rescue treatment for metabolic acidosis (low bicarbonate)	acidosis (low bicarbonate) between SZC and placebo
• To evaluate the efficacy of SZC as compared to placebo in normalizing sK+ and increasing serum bicarbonate in patients with hyperkalemia and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) without need for rescue treatment for hyperkalemia or metabolic acidosis (low bicarbonate). • Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive and bicarbonate ≥22 mmol/L	• Null: No difference in the occurrence of patients achieving normokalemia and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to Day 29 or mean serum bicarbonate >22 mmol/L at Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) or hyperkalemia between SZC and placebo
• To describe the need for rescue treatment with sodium bicarbonate for metabolic acidosis (low bicarbonate) in SZC and placebo arms	• Occurrence (yes/no) of patients needing rescue treatment for low sodium bicarbonate any time during the randomized phase	• Null: No difference in the occurrence of patients needing rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo
Safety		

• To evaluate the safety and tolerability of SZC as compared to placebo in patients with hyperkalemia and metabolic acidosis associated with CKD	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, and ECG. Assessments related to AEs cover:
	  • Occurrence/frequency
	  • Relationship to SZC/placebo as assessed by investigator
	  • Intensity
	  • Seriousness
	  • Death
		• Not applicable

Objectives	Endpoints	Hypotheses
	• AEs leading to discontinuation of SZC/ placebo	

Abbreviations: AE = adverse event; CKD = chronic kidney disease; ECG = electrocardiogram; EOT = end of treatment; sK+ = serum potassium; SZC = sodium zirconium cyclosilicate.

For the CCI endpoints, and hypotheses, see Section 3 of the protocol.

Overall Design

This is a prospective, randomized, double-blind, placebo-controlled, parallel, multicenter, Phase IIIb study to investigate the safety and efficacy of SZC in patients with hyperkalemia and low bicarbonate (or metabolic acidosis).

The study will be conducted in the United States (US) at approximately 35 investigative sites.

After screening on Day 1, all patients will receive open-label SZC for up to 48 hours, and then be randomized to double-blind treatment of SZC or placebo for 4 weeks. Follow-up will continue for 7 days after the last administration of study medication.

Disclosure Statement: This is a parallel-group treatment study with 2 arms that is participant- and investigator-blinded.

Number of Participants:. Approximately 477 patients will be screened. Approximately 148 patients will be enrolled to the open-label phase of the study to achieve 136 randomly assigned to study intervention.

Intervention Groups and Duration

This study consists of a short screening period (Day 1), an open-label correction phase (up to 48 hours), a 4-week randomized treatment phase, and a follow-up period (7 days after the last administration of study medication). The total study treatment period consisting of open-label and randomized phases will be 28 days.

Screening will be performed using potassium and bicarbonate values from a study-approved point-of-care blood analyzer (Point-of-Care-Test, POCT), to determine eligibility of consenting patients to enter the open-label correction phase. Patients who meet the POCT eligibility criteria of serum potassium (sK+) between 5-5.9 mmol/L inclusive, AND serum bicarbonate between 16-20 mmol/L inclusive, will be enrolled into the open-label correction phase. All baseline parameters should be measured/collected prior to administration of the first dose of study drug in the open-label initial phase.

In the open-label initial phase, patients will receive open-label SZC orally at a dose of 10 g

three times daily (TID) for up to 48 hours, depending on POCT potassium value..

Patients who achieve normokalemia (POCT K+ between 3.5 and 5.0 mmol/L inclusive) within 48 hours will be randomized 1:1 into the double-blind randomized treatment phase to receive 10 g SZC or placebo once daily (QD) starting dose for the following 26 or 27 days. Patients who achieve normokalemia after 24 hours will be randomized and will not need to continue on 10 g SZC TID for another 24 hours.

Study treatment will end with the Day 29 visit, which will be followed by the Follow-up Phase visit, 7 days after the last administration of study medication.

Data Monitoring Committee: No

Statistical Methods

The analysis of the primary endpoint will be conducted according to the intention-to-treat principle using the full analysis set (FAS). All randomized patients will be included in the analyses, irrespectively of whether they do, or do not, receive treatment or do, or do not, experience a particular type of protocol deviation, such as failure to fulfill one or more eligibility criteria. Thus, the population under study consists of all patients who are deemed as suitable for randomization by the investigator(s).

The primary endpoint is a classification of each randomized patient into a responder or a non-responder category (ie, a 0-1 type of response), with a patient being a responder if they:

a. Are normokalemic (central laboratory sK+ between 3.5 and 5.0 mmol/L inclusive) at the EOT visit (Day 29)
b. Did not receive any rescue therapy for hyperkalemia during the randomized phase

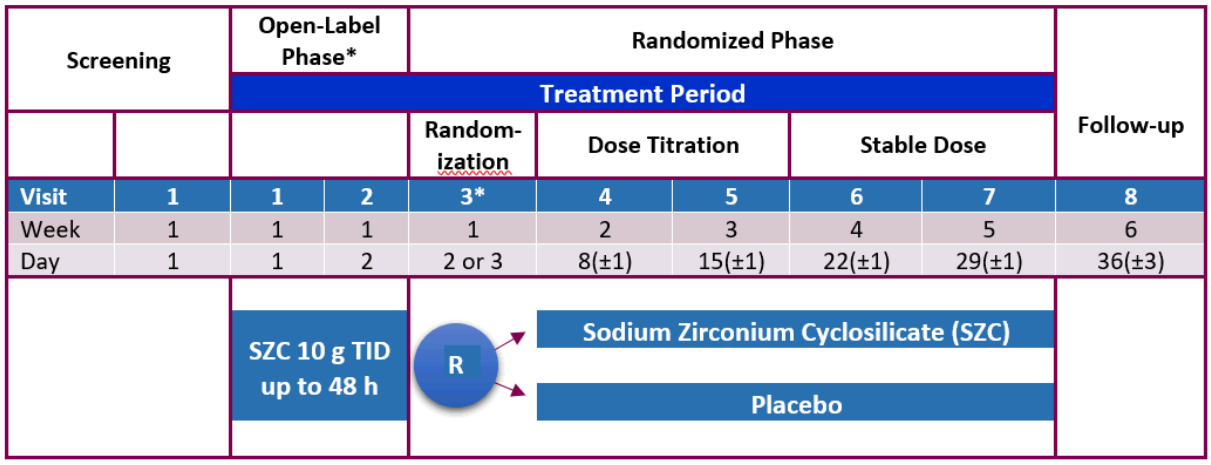
The following rules will be implemented to account for missing laboratory results:

a. If Visit 7 central laboratory sK+ is missing, then Visit 6 central laboratory sK+ will be used in its place (last observation carried forward [LOCF]).
b. If central laboratory sK+ is missing for Visits 6 and 7, then sK+ will be replaced by POCT value adjusted to reflect the mean difference between POCT and sK+ values from all available paired laboratory samples. (Visit 7 POCT will be used unless missing, in which case Visit 6 POCT will be used.)
c. If no results (central laboratory sK+ or POCT K+) are available for Visits 6 and 7, then classify as non-evaluable.

A sensitivity analysis will be conducted based on the Per Protocol Set (PPS). Additional sensitivity analyses will also be carried out related to the proportion of patients achieving normokalemia in the SZC versus placebo arm.

1.2 Schema

Figure 1 Study design



* Open-label phase will be Day 1 or Days 1 and 2. Randomization to double-blind placebo-controlled phase will start Day 2 or 3.

[#] Visit 3 procedures will occur on Day 2 for patients who achieve normokalemia (POCT K+ 3.5-5.0 mmol/L) at Visit 2 (Day 2) and on Day 3 for patients who achieve normokalemia at Visit 3. Patients who achieve normokalemia at 24 hours will not need to remain on SZC 10 g TID and will be enrolled in the randomized placebo-controlled phase at Day 2. Patients who achieve normokalemia at 48 hours will be enrolled in the randomized placebo-controlled phase at Day 3.
Patients with POCT K+ <3.5 mmol/L at Day 2 or 3 and patients with POCT K+ >5.0 mmol/L at Day 3 will be discontinued from the study and followed up as per protocol.

Abbreviations: h = hours; K+ = potassium; R = randomization; SZC = sodium zirconium cyclosilicate; TID = three times daily.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening	Open-Label Phase (up to 2 days)[a]		Randomized Phase (Visit 2 or 3 to Visit 7)					E/D	Follow-up Phase	Details in CSP section
Visit	**1**	**1**	**2**	**Randomization (Day 2 or 3)**	**4**	**5**	**6**	**7 (EOT)**		**8**	
			2	**3** [a]							
Week	**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**		**6**	
Day (Window)	**1**	**1**	**2**	**2 or 3**	**8(±1)**	**15(±1)**	**22(±1)**	**29(±1)**		**36(±3)**	
Informed consent	X										Section 5.1
Inclusion and exclusion criteria	X										Sections 5.1 & 5.2
Routine Clinical Procedures											
Demography	X										Section 5.1
Physical examination (including height[b])	X								X	X	Section 8.2.1
Medical history	X										Section 5.2
Concomitant medication	At every visit and may be conducted by phone if not tied to a visit										Section 6.8
Vital signs	X			X	X	X	X	X	X	X	Section 8.2.2
Weight	X			X	X	X	X	X	X	X	Section 8.2.1
Routine Safety Measurements											
Adverse events	At every visit and may be conducted by phone if not tied to a visit										Section 8.3
Urine pregnancy test (females only)	X										Section 8.2.4
Clinical safety laboratory assessments (including urine dipstick)[c]	X			X				X	X	X	Section 8.2.4
Electrocardiogram	X			X				X	X	X	Section 8.2.3
Efficacy Lab Assessments[d]											
Central laboratory potassium, bicarbonate, and chloride[e]	(X)[e]			(X)	X	X	X	(X)	(X)	(X)	Section 8.2.4

POCT assessments [f]	X		X	X	X	X	X	X	X	X	Section 8.2.4
Spot urine (central lab) [g]		X		X	X	X	X	X	X	X	Section 8.1.4
CCI [redacted]	[redacted]			[redacted]				[redacted]	[redacted]	[redacted]	[redacted]
Optional genomics blood sample	X[h]										Section 8.7
Study Treatment Administration											
Drug dispensation open-label phase		X	X								Section 6.1
Drug dispensation randomized phase				X	X	X	X				Section 6.2
Randomization (1:1 SZC or placebo)				X							Sections 6.2-6.3
Titration, if needed					X	X	X[i]				Section 6.2

Abbreviations: CSP = clinical study protocol; E/D = Early Study Intervention/Discontinuation; EOT = end of treatment; K+ = potassium; SZC = sodium zirconium cyclosilicate; TID = three times daily; UACR = urine albumin-to-creatinine-ratio.

a Open-label will be Day 1 or Days 1 and 2; randomization will start Day 2 or 3. Visit 3 procedures will occur on Day 2 for patients who achieve normokalemia (POCT K+ between 3.5-5.0 mmol/L inclusive) at Visit 2 (Day 2) and on Day 3 for patients who achieve normokalemia at Visit 3. Patients who achieve normokalemia at 24 hours will not need to remain on SZC 10 g TID and will be enrolled in the randomized placebo-controlled phase at Day 2. Patients with POCT K+ <3.5 mmol/L at Day 2 or 3 will be discontinued from the study and followed up as per protocol. Patients who achieve normokalemia at 48 hours will be enrolled in the randomized placebo-controlled phase at Day 3. Patients with POCT K+ >5.0 mmol/L at Day 3 will be discontinued from the study and followed up as per protocol.

b Height will be collected only at the screening visit.

c Clinical safety laboratory assessments at screening to be drawn at the same timepoint as POCT. Drawn samples will be discarded if patient does not meet criteria for enrolment into open label phase.

d Fasting is recommended (but not mandatory) as meals can transiently change acid-base status.

e Potassium, bicarbonate, and chloride will be measured as part of the clinical safety laboratory assessments for Visits 1, 3, 7, and 8.

f POCT assessment will include bicarbonate as total carbon dioxide (TCO2), potassium, creatinine, sodium, chloride, and anion gap.

g Urinary albumin, ammonium, citrate, pH, creatinine, anion gap, and calculated UACR and ammonium-to-creatinine ratio will be measured at the central laboratory.

h Optional genomics sample to be drawn at the same timepoint as the second POCT. Drawn samples will be discarded if patient does not meet criteria for enrolment into open label phase.

i A stable dose of SZC/placebo is recommended during the last 2 weeks of the randomized phase. However, dose titration will be allowed for optimal patient care and/or if risk for discontinuation or as per investigator judgment, according to Section 6.3.

2 INTRODUCTION

Sodium zirconium cyclosilicate (SZC) is as an orally-administered, non-polymer non-absorbable, inorganic, crystalline cation-exchanger that represents a novel therapy for hyperkalemia. It selectively binds potassium in exchange for hydrogen and sodium ions throughout the gastrointestinal (GI) tract, thereby reducing serum potassium (sK+) concentration.[1,2] The potassium is removed from the body through fecal excretion.

The efficacy of SZC to rapidly correct hyperkalemia and maintain normokalemia irrespective of underlying morbidity, and its favorable safety profile, have been well documented in the clinical program. In clinical studies, three times daily (TID) administration of 10g SZC rapidly normalizes sK+ (between 3.5 and 5.0 mmol/L inclusive) within 48 hours[3,4,5] and is associated with maintenance of normokalemia for up to 1 year with continued administration of titrated SZC dose.[6]

SZC treatment has also been associated with dose-dependent increases in serum bicarbonate based on existing data including Phase II, open-label Phase III, and post-hoc analyses of randomized Phase III trials.[1,2,3]

2.1 Study Rationale

A significant proportion of patients with chronic kidney disease (CKD) and hyperkalemia have low serum bicarbonate. Based on recent studies, low serum bicarbonate and associated metabolic acidosis have been associated with an increased risk for CKD progression, metabolic bone disease, and mortality; and recent evidence has bolstered the need to increase serum bicarbonate.[7]

Post-hoc analyses of Phase III studies for SZC showed a dose-dependent increase in serum bicarbonate and the increase was greater in patients with lower serum bicarbonate at baseline.[1,8]

However, patients in SZC studies were included on the basis of their elevated POCT or sK+; serum bicarbonate level was not part of the inclusion criteria.[1,4,5] Though a portion of the patients in the studies (39.4% in ZS-004 and 31.4% in ZS-005) also had a low serum bicarbonate, the population of CKD patients with hyperkalemia and low serum bicarbonate was not systematically identified or studied. In addition, these studies did not:

a. restrict use of sodium bicarbonate, thus confounding the effect of SZC on serum bicarbonate; OR
b. evaluate the impact of SZC on urine ammonium excretion.

Therefore, the full benefit of SZC in patients with hyperkalemia and metabolic acidosis associated with CKD is not known.

A double-blind randomized study that demonstrates SZC's ability to treat hyperkalemia and increase serum bicarbonate in this patient population could potentially improve health and reduce the complexity of care management. Measuring change in urine ammonium will further elucidate the mechanism behind the increase in serum bicarbonate seen with SZC. This study aims to investigate if SZC can increase serum bicarbonate in a clinically meaningful way. Increases in serum bicarbonate with SZC treatment may provide potential benefits in terms of correcting metabolic acidosis, as well as reducing the need for alkali supplementation with sodium bicarbonate.

2.2 Background

Metabolic acidosis associated with CKD is defined as a serum bicarbonate <22 mmol/L (per KDIGO guidelines)[9] and occurs in about 1 in 3 patients with CKD stage 3-5 with hyperkalemia.[10] An even larger proportion of CKD patients have a negative acid balance despite having serum bicarbonate levels ≥22 mmol/L;[11] therefore, the optimal serum bicarbonate level in CKD remains to be determined. Recent studies suggest treatment of metabolic acidosis by increasing serum bicarbonate appears to improve muscle mass and preserve kidney function by decreasing protein catabolism and may slow progression of CKD.[7,12]

However, current treatment with sodium bicarbonate is limited by high pill burden needed to correct the serum bicarbonate.[7] Given the evidence that SZC treats hyperkalemia and also causes a dose-dependent increase in serum bicarbonate, patients with both these electrolyte/acid-base complications may observe efficacy from treatment with SZC.

In post-hoc analysis of ZS-004, patients with a baseline serum bicarbonate level of <22 mmol/L observed mean increase in serum bicarbonate of 5.1 mmol/L at Day 29 with SZC versus 1.5 mmol/L increase for placebo ($p<0.001$).[2,3] In ZS-005, a mean increase in serum bicarbonate of 2.5 mmol/L was observed at Day 29 in patients with baseline serum bicarbonate <22 mmol/L compared to a 0.77 mmol/L increase in all patients.[1]

The exact mechanism behind the increase in serum bicarbonate seen with SZC has not been fully elucidated. There are 2 potential mechanisms: a) correction of hyperkalemia leads to increased renal ammoniagenesis effectively increasing renal excretion of acid[6,13] or b) SZC binds ammonium ions in the GI tract, given that the mean binding site is 3 Angstroms and the size of ammonium is 2.96 Angstroms in the dehydrated form. This leads to less ammonium absorption from the GI tract which would otherwise be metabolized to urea, a process that consumes bicarbonate.[14,15] A pathways analysis evaluating the 2 potential mechanisms using data from prior SZC studies shows that serum urea levels decreased and urine pH is slightly increased. The mechanism responsible for an increase in serum bicarbonate could be related to, at least in part, SZC binding ammonium in the GI tract.[16] Prior SZC studies have not studied the impact of SZC on urine ammonium. If the urine ammonium does not increase

markedly with SZC, that would suggest that the mechanism of the correction of hyperkalemia is related to an increased excretion of ammonium in the GI tract. Additional confirmatory studies, eg, measurement of fecal ammonia, will be needed. Such evidence would differentiate SZC from other potassium binders, as an increase in serum bicarbonate was not seen in the patiromer clinical trials.[17]

A detailed description of the chemistry, pharmacology, efficacy, and safety of SZC is provided in the Investigator's Brochure (IB)[8]. Benefit/Risk Assessment

This study will recruit patients who have mild-to-moderate hyperkalemia. There is a risk of hyperkalemia in those patients who are randomized to placebo and risk of hypokalemia in patients randomized to SZC. Additionally, there is theoretical risk of worsening metabolic acidosis (low bicarbonate). Hence, hyperkalemia, hypokalemia, and potentially worsening metabolic acidosis are the major medical risks for patients participating in this trial. The following study design features were included to minimize the risk to patients:

- All patients will receive active treatment with SZC (10 g TID, up to 48 hours) during the open-label phase and only patients that have normalized POCT K^+ will be randomized into the study, minimizing the risk of hyperkalemia in the randomized treatment phase.
- POCT will be used by sites to measure K+ and bicarbonate at each visit, providing investigators with up-to date K+ and bicarbonate measurements thereby allowing dose adjustments/discontinuation to occur as appropriate during the study visit.
- SZC dose titration and stopping rules and rescue therapy rules based on POCT K+ monitoring are included in this protocol to minimize the risk of hyperkalemia and hypokalemia.
- The risk of severe hyperkalemia upon randomization to placebo will be mitigated with close monitoring of K+ from the beginning of the randomized treatment through the EOT visit.
- The risk of hyperkalemia after the EOT visit will be mitigated by monitoring of K+ for 1-week post-study conclusion.
- Hypokalemia has been reported with SZC. SZC dose titration and stopping rules based on K+ monitoring are included in this protocol to minimize the risk of hypokalemia in patients receiving SZC.
- Rules for rescue medication treatment based on POCT bicarbonate monitoring are included in the protocol to minimize the risk of severe metabolic acidosis.
- Edema-related events (grouped terms include preferred terms of edema, edema peripheral, generalized edema, fluid overload, fluid retention, hypervolemia, localized edema, and peripheral swelling) have been reported by patients treated with SZC, in

particular at higher doses. Physical examinations to assess edema will be performed and the patient will be weighed at prespecified visits to ensure development of edema will be detected early and appropriately managed (see Section 8.2.1).

More detailed information about the known and expected benefits and potential risks of SZC may be found in the IB.[8]

2.2.1 Risk Assessment

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Common (≥1/100 to <1/10) ADR observed in SZC clinical studies: edema-related events	Edema-related events were reported by 5.7% of SZC subjects; 2.7%, 5.2%, 14.3%, and 1.7% of subjects randomized to SZC 5 g, 10 g, 15 g, and placebo, respectively. Grouped terms include preferred terms of Edema, Edema peripheral, Generalized edema, Fluid overload, Fluid retention, Hypervolemia, Localized edema, and Peripheral swelling. (Refer to IB Section 5.4-5.5 and 6.4)	Of the edema-related events, 53% were managed with initiating diuretic treatment or adjusting the diuretic dose, while the remainder did not require treatment.
Common (≥1/100 to <1/10) ADR observed in SZC clinical studies: hypokalemia	Hypokalemia (serum K+ <3.5 mmol/L), a result of the pharmacological action of the drug, was observed in 4.1% of subjects treated with SZC.	Resolved with dose adjustment or discontinuation of SZC treatment.

Abbreviations: ADR = adverse drug reaction; IB= Investigator's Brochure; QD = once daily; sK+ = serum potassium; SZC = sodium zirconium cyclosilicate

2.2.2 Benefit Assessment

Clinical studies in patients with hyperkalemia have demonstrated the efficacy and safety of SZC in the correction of hyperkalemia and maintenance of normokalemia.

Participants, irrespective of their treatment allocation, may benefit from more intense monitoring and attention to their underlying condition. Patients randomized to SZC may benefit by being able to maintain normokalemia according to recommended target doses of SZC. In the larger perspective, the main potential benefit of conducting this study lies in the possibility to generate scientific evidence for improved management of patients with hyperkalemia and metabolic acidosis associated with CKD, and potentially improve health

and reduce the complexity of care management.

2.2.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with SZC are justified by the anticipated benefits that may be afforded to participants with hyperkalemia and metabolic acidosis.

In previous studies, SZC has proven to effectively and safely correct hyperkalemia to the normal sK+ range and maintain normokalemia for up to 12 months in a broad patient population with hyperkalemia, including those on hemodialysis. In these studies, treatment with SZC was associated with dose-dependent increases in serum bicarbonate. Unfavorable effects were limited, and the adverse drug reactions (ADRs) of edema-related events and hypokalemia were generally mild and easily managed. Dose titration during maintenance treatment allows individualized treatment to maintain normokalemia. Based on the available clinical data, the benefit/risk assessment is favorable for correction of hyperkalemia with SZC 10 g TID for up to 2 days, and for maintenance treatment of patients with hyperkalemia across the dose range 5 g every other day (QOD) to 5 to 15 g QD. Data from these studies demonstrate that the majority of patients can be adequately maintained on the 5 g QD or 10 g QD dose. Based on the limited potential risks to study participants, the risk mitigations included in this protocol, and the long-term potential benefits of simplifying management of patients with hyperkalemia and metabolic acidosis associated with CKD, it is concluded that the study as proposed exposes recruited patients to an acceptable risk.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints	Hypotheses
Primary		
• To evaluate the efficacy of SZC as compared to placebo in maintaining normal sK+ in patients with hyperkalemia and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT without need for rescue treatment for hyperkalemia at any point during the randomized phase	• Null: No difference in the occurrence of patients having a normal sK+ on Day 29 without need for rescue treatment for hyperkalemia at any point during the randomized phase between SZC and placebo
Secondary		
• To evaluate the efficacy of SZC as compared to placebo in increasing serum bicarbonate in patients with hyperkalemia and metabolic acidosis associated with CKD	• Mean change in serum bicarbonate at Day 29 compared to baseline (Day 1) • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to EOT (Day 29) without need for rescue treatment for metabolic acidosis (low bicarbonate) • Occurrence (yes/no) of patients having serum bicarbonate ≥22 mmol/L • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥2 mmol/L from baseline (Day 1) to EOT without need for rescue treatment for metabolic acidosis (low bicarbonate)	• Null: No difference in mean change in serum bicarbonate from baseline (Day 1) to Day 29 between SZC and placebo • Null: No difference in the occurrence of patients having an increase in serum bicarbonate of ≥2 mmol/L or ≥3 mmol/L from baseline (Day 1) to Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo
• To evaluate the efficacy of SZC as compared to placebo in normalizing sK+ and increasing serum bicarbonate in patients with hyperkalemia and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) without need for rescue treatment for metabolic acidosis (low bicarbonate) or hyperkalemia	• Null: No difference in the occurrence of patients having normokalemia and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to Day 29 or mean serum bicarbonate ≥22 mmol/L at Day 29 without need for rescue treatment for hyperkalemia or metabolic acidosis (low

Objectives	Endpoints	Hypotheses
	• Occurrence (yes/no) of patients having a normal sK+ between 3.5 and 5.0 mmol/L inclusive and bicarbonate ≥22 mmol/L at Day 29 without need for rescue treatment for hyperkalemia or metabolic acidosis (low bicarbonate)	bicarbonate) between SZC and placebo
• To describe the need for rescue treatment with sodium bicarbonate for metabolic acidosis (low bicarbonate) in SZC and placebo arms	• Occurrence (yes/no) of patients needing rescue treatment for low sodium bicarbonate any time during the randomized phase	• Null: No difference in the occurrence of patients needing rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo
Safety		
• To evaluate the safety and tolerability of SZC as compared to placebo in patients with hyperkalemia and metabolic acidosis associated with CKD	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, and ECG. Assessments related to AEs cover: • Occurrence/frequency • Relationship to SZC/placebo as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of SZC/ placebo	• Not applicable

CCI

Abbreviations: AE = adverse event; CKD = chronic kidney disease; ECG = electrocardiogram; EOT = end of treatment; sK+ = serum potassium; SZC = sodium zirconium cyclosilicate.

4 STUDY DESIGN

4.1 Overall Design

NEUTRALIZE is a Phase IIIb multicenter, placebo-controlled, randomized, double-blind, parallel-designed clinical trial which includes a screening visit, a treatment period (approximately 4 weeks), and an off-treatment follow-up visit 1 week later. The treatment period will be divided into an open-label correction phase of up to 48 hours' duration where all patients will receive SZC followed immediately by a randomized, placebo-controlled phase from Day 3 to Day 29.

4.1.1 Open-label Correction Phase

All patients fulfilling inclusion/exclusion criteria will enter the initial open-label correction phase and receive SZC. During the correction phase, the dose of SZC will be 10 g TID up to 48 hours. Patients meeting normokalemia (POCT K+ between 3.5 and 5.0 mmol/L inclusive) at Day 2 (after 24 hours in the open-label correction phase) will be eligible for the randomized phase. Patients not meeting normokalemia at Day 2 will continue in the open-label correction phase for an additional 24 hours and repeat POCT on the next day (Day 3). If normokalemia is achieved on Day 3, the patient is eligible for the randomized phase. If normokalemia is not achieved (POCT K+ value is ≥5.1 mmol/L), the patient will have treatment discontinued, be withdrawn from the study, and complete follow-up per the Schedule of Activities (SoA). Patients with POCT K+ <3.5 mmol/L at Day 2 or 3 will be discontinued from the study and followed up as per protocol.

4.1.2 Randomized Placebo-controlled Phase

Patients who achieve normokalemia (defined as POCT K+ between 3.5 and 5.0 mmol/L inclusive) after receiving SZC 10 g TID for up to 48 hours during the open-label correction phase will be randomized 1:1 to receive either SZC or placebo in the 4-week double-blind, placebo-controlled phase. Patients will be randomized to SZC 10 g QD or placebo 10 g QD. The dose of SZC/placebo will be titrated by increasing or decreasing the dose by 5 g increments at 1-week intervals to between 5 g every other day (QOD) and 15 g QD during the first 2 weeks of the randomized phase to maintain normokalemia by POCT K+. A stable SZC/placebo dose is recommended during the last 2 weeks of the randomized placebo-controlled phase (see Section 6.3).

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Patient Population

The study will exclusively recruit patients who have hyperkalemia and low serum bicarbonate associated with CKD. The study will examine the effect of SZC, a commercially available drug with the indication for treatment of hyperkalemia, on increasing serum bicarbonate. Currently, there are no approved single agents shown to treat both hyperkalemia and raise

serum bicarbonate.

Eligible patients will undergo an open-label period of treatment with SZC 10 g TID for up to 48 hours to normalize K+ (on-label dosing). This methodology has been used in other SZC trials for this patient population. POCT K+ levels will be monitored during the open-label period and those who normalize the K+ level will be eligible to be randomized; those who do not normalize K+ will not be eligible for randomization.

4.2.2 Rationale for Blinding and Randomization

The study employs blinding to minimize the risk for bias introduced by patients, investigators, and sponsor or sponsor representatives. Minimizing bias introduced by investigators and patients is imperative as the primary and secondary endpoints of the trial can be influenced significantly by treatment choices made by the investigators in the trial and agreed with participating patients. Randomization is employed to minimize the risk for bias and produce comparable groups, and a 1:1 randomization scheme was selected to maximize power and thereby minimize the number of patients needed to be recruited.

4.2.3 Rationale for Treatment Groups

The treatment groups for this Phase IIIb study include SZC and placebo groups. Both groups will have K+ normalized at the beginning of the randomized trial and close monitoring of K+ and bicarbonate will occur during the duration of the study. Titration will occur during the first 2 weeks of therapy to achieve optimal study drug dose according to Sections 6.2 and 6.3. Titration of SZC will be based on POCT K+ values at each visit to ensure patients receive SZC at an individually optimized dose. Patients randomized to receive placebo will undergo mock titration to maintain the study blinding. A similar methodology has been used in other SZC trials for similar study populations with maintenance of normokalemia. Clear guidance is in place for rescue therapy for both hyperkalemia (>6.0 mmol/L) and low serum bicarbonate (≤15 mmol/L) as well as for study discontinuation.

Placebo is used as comparator in NEUTRALIZE as the primary and secondary efficacy endpoints could be affected by treating physicians knowing the treatment allocation of individual patients, and as there is no drug currently approved to treat patients with hyperkalemia associated with CKD and to raise their serum bicarbonate.

4.2.4 Rationale for Objectives and Endpoints

NEUTRALIZE is a Phase IIIb study, and as such it is designed to provide necessary and sufficient data to determine if there is an additional benefit of increasing serum bicarbonate in patients with hyperkalemia associated with CKD. The primary objective is to evaluate the efficacy of SZC as compared to placebo in maintaining normal sK+ in patients with hyperkalemia and metabolic acidosis associated with CKD. Secondary endpoints will focus on the ability of SZC to raise serum bicarbonate. CCI

CCI

4.3 Justification for Dose

In non-dialysis patients, the approved SZC dose in the US for correction of hyperkalemia is 10 g TID taken orally for up to 48 hours. For maintenance of normokalemia, a dose of 10 g QD is approved, and can be adjusted at 1-week intervals as needed (by 5 g increments) to obtain desired sK+ target range (between 3.5 and 5.0 mmol/L inclusive). The recommended maintenance dose range is from 5 g QOD to 15 g QD.

Clinical studies in patients with hyperkalemia consistently demonstrated that initial open-label treatment with SZC 10 g TID for 24 hours up to 48 hours resulted in clinically meaningful sK+ reduction with a majority of patients achieving normokalemia within 24 to 48 hours. Moreover, patients with higher baseline sK+ levels had greater reductions in sK+ levels. Onset of efficacy was rapid with sK+ reduction observed as early as 1 hour after dose intake.

After correction of hyperkalemia, continued maintenance treatment for 28 days with SZC 5 g, 10 g, or 15 g QD resulted in continued effective control of sK+ within the normokalemic range. The proportion of patients who remained normokalemic at EOT with SZC 5 g, 10 g, and 15 g QD increased dose-dependently (range: 71% to 85%) and was superior to placebo. In addition, long-term maintenance treatment of up to 12 months with SZC utilizing a dose titration scheme with the starting dose of 5 g QD or 10 g QD, titrated to a maximum of 15 g QD or a minimum of 5 g QOD was effective in maintaining normokalemia in the majority of patients.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study or if he/she received rescue treatment for hyperkalemia or low serum bicarbonate including the last scheduled procedure shown in the SoA (Table 1).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

1 Participant must be 18 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants with stage 3-5 CKD and not on dialysis, with an estimated glomerular filtration rate (eGFR) ≤59 mL/min/m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

3 POCT K+ level >5 mmol/L to ≤5.9 mmol/L and POCT bicarbonate levels between 16-20 mmol/L inclusive prior to the first SZC dose on study Day 1

4 Ability to have repeated blood draws or effective venous catheterization.

Sex

5 Male and/or female.

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

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

Informed Consent

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

7 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative. The patient may opt out on the genomic blood sample.

5.2 Exclusion Criteria

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

Medical Conditions

1 Participants with pseudohyperkalemia.

2 Dialysis requirement or anticipated by the investigator to require dialysis therapy within 1 month, history of renal transplant, or life expectancy less than 3 months.

3 Cardiac arrhythmias requiring immediate treatment.

4 Active or suspected diabetic ketoacidosis.

5 POCT bicarbonate low enough to need emergency intervention or treatment as judged by the investigator.

6 Acute/chronic worsening renal function (eg, ≥30% decline in eGFR) in the 3 months before screening.

7 Current acute decompensated HF, hospitalization due to decompensated HF within 4 weeks prior to screening, or myocardial infarction (MI), unstable angina, stroke or transient ischemic attack (TIA) within 12 weeks prior to screening.

8 Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or valvular repair/replacement within 12 weeks prior to screening or planned to undergo any of these operations.

9 Symptomatic hypotension.

10 Current exacerbation of chronic obstructive pulmonary disease (COPD)/asthma or hospitalization due to exacerbation of COPD/asthma within 4 weeks of screening.

11 Severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders..

12 Active malignancy requiring treatment.

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

14 Congenital long QT syndrome.

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

16 QTcF (QT interval corrected by the Fridericia method) >550 msec.

Prior/Concomitant Therapy

17 Active treatment (within 7 days prior to screening) with SZC, sodium bicarbonate, sodium polystyrene sulfonate, lactulose, or patiromer.

Prior/Concurrent Clinical Study Experience

18 Participation in another clinical study with an investigational product (IP) administered in the last month[1].

19 Participants with a known hypersensitivity to SZC.

Other Exclusions

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

21 Patients who are severely physically or mentally incapacitated and who in the opinion of the investigator are unable to perform the patients' tasks associated with the protocol.

22 Previous enrolment in the present study.

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

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

5.3 Lifestyle Considerations

No lifestyle restrictions are required in the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but fail inclusion/exclusion criteria and are not entered into the open-label correction phase. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after ≥2 weeks if screen failure was due to patient not meeting inclusion criterion #3 (POCT K+ level >5 mmol/L to ≤5.9 mmol/L and POCT bicarbonate levels between 16-20 mmol/L) and/or met exclusion criterion #24 [if the participant has evidence of COVID-19 infection within 2 weeks prior to screening]). Further, participants who failed due to not meeting inclusion criteria #3 may be rescreened more than once at investigator's discretion if sK+ and bicarbonate obtained during routine patient care subsequent to the last screening are consistent with screening criteria. Rescreened participants should be assigned the same participant number as the initial screening.

[1] Participants who received a COVID-19 vaccine whilst still under Emergency Use Utilization will not be excluded from the study.

6 STUDY INTERVENTION

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

6.1 Open-label Correction Phase (Visits 1 and 2)

All eligible patients will receive SZC 10 g TID for up to 48 hours. Patients with POCT K+ ≥5.1 mmol/L at Visit 2 will continue on SZC 10 g TID for another 24 hours. Patients who achieve normokalemia (POCT K+ between 3.5 and 5.0 mmol/L inclusive) at Visit 2 will proceed to randomization. Patients with POCT K+ <3.5 mmol/L at any time during the open-label phase will be withdrawn from study treatment and will be followed per protocol.

Open-label phase failures are defined as participants who enter the open-label correction phase and receive at least 1 dose of SZC but who fail to achieve normokalemia (POCT K+ between 3.5 and 5.0 mmol/L inclusive) after the 48-hour correction phase. Individuals who fail the open-label phase will not be eligible to be rescreened.

6.2 Randomized Placebo-controlled Phase (Visits 3 to 5)

Patients who achieve normokalemia during the open-label correction phase will be randomized in a 1:1 double-blind fashion to SZC 10 g QD or placebo 10 g QD. Dose can be titrated during the first 2 weeks of the randomized phase based on POCT K+. Table 4 describes the titration of SZC and placebo and discontinuation criteria for abnormal K+ during the first 2 weeks of the randomized phase.

Table 4 Dose Titration and Discontinuation Criteria During the Randomized Placebo-controlled Phase: first 2 weeks

Note: If needed, dose titrations will be made on Day 8 and Day 15 (Visits 4 and 5).

SZC/Placebo	POCT K+ (mmol/L) on Day 8 or 15	Dose Titration and Discontinuation Criteria for Abnormal K+
SZC/placebo: All patients start on 10 g QD, then titrate from there based on POCT K+	<3.0	• Treatment permanently discontinued. Obtain ECG and treat according to medical judgment.
	3.0 - 3.4	• Obtain ECG, permanently discontinue treatment if serious arrhythmia found and treat according to medical judgment. • If no serious arrhythmia found, pause treatment and treat according to medical judgment. • Increase monitoring until POCT K+ ≥3.5 mmol/L. • Evaluate for underlying risk for hypokalemia. If hypokalemia resolves and patient deemed appropriate to restart treatment, then initiate SZC/placebo 5 g QOD for the rest of the treatment period.

SZC/Placebo	POCT K+ (mmol/L) on Day 8 or 15	Dose Titration and Discontinuation Criteria for Abnormal K+
	3.5 - 5.0	• No change in SZC/placebo dose.
	5.1 – 5.5	• Increase SZC/placebo dose by 5 g QD increments up to a maximum of 15 g QD.*
	5.6 – 6.0	• Obtain ECG, discontinue treatment if serious arrhythmia found. • If no serious arrhythmia, increase SZC/placebo dose by 5 g QD increments up to a maximum of 15 g QD.* • Further K+ monitoring and treatment per investigator medical judgment based on patient risk and benefit. • Increase monitoring frequency until K+ ≤5.5 mmol/L.
	>6.0	• Treatment permanently discontinued; initiate rescue treatment (see Section 6.8.1 for rescue treatment). • Obtain ECG and treat according to medical judgment.

* Uptitration (based on K+ levels) will occur at 1-week intervals.

6.3 Randomized Placebo-controlled Phase (Visits 6 and 7)

A stable dose of SZC/placebo is recommended during the last 2 weeks of the randomized phase. However, dose titration will be allowed for optimal patient care and/or if risk for discontinuation or as per investigator judgment. Patients with POCT K+ excursions outside of between 3.5 and 5.0 mmol/L inclusive during the last 2 weeks of the randomized phase (Days 16-28) will be managed as detailed in Table 5.

Table 5 Discontinuation Criteria During the Randomized Placebo-controlled Phase: last 2 weeks

SZC/Placebo	POCT K (mmol/L), Day 22	Discontinuation Criteria for Abnormal K+
SZC/placebo	<3.0	• Treatment permanently discontinued. Obtain ECG and treat according to medial judgment.
	3.0 - 3.4	• Obtain ECG, discontinue treatment if serious arrhythmia found and treat according to medical judgment. • If no serious arrhythmia found, temporarily interrupt treatment and treat according to medical judgment. • Increase monitoring until POCT K+ ≥3.5 mmol/L. • Evaluate for underlying risk for hypokalemia. If hypokalemia resolves and patient is deemed appropriate to restart treatment, then initiate SZC/placebo 5 g QOD for the rest of the treatment period.
	3.5 - 5.5	• No change in SZC/placebo dose.

SZC/Placebo	POCT K (mmol/L), Day 22	Discontinuation Criteria for Abnormal K+
	5.6 – 6.0	• No change in SZC/placebo dose except for optimal patient care and/or if risk for discontinuation or as per investigator judgment. • Obtain ECG, permanently discontinue treatment if serious arrhythmia found. • Further K+ monitoring and treatment per investigator medical judgment* based on patient risk and benefit. • Increase monitoring frequency until K+ ≤5.5 mmol/L.
	>6.0	• Treatment permanently discontinued, initiate rescue treatment (see Section 6.8.1 for rescue treatment). • Obtain ECG and treat according to medical judgment.

* Could include rescue therapy or discontinuation from study treatment. To be followed up and recorded as per protocol.

6.4 Study Intervention(s) Administered

During the open-label correction phase, all patients will receive SZC orally at a dose of 10 g TID for a maximum of 6 doses over 48 hours. Study drug will be administrated orally with or without food. The individual kit will be assigned through Interactive Response Technology/Randomization and Trial Supply Management (IRT/RTSM).

For patients with POCT K+ values within the normokalemic range (between 3.5 to 5.0 mmol/L inclusive) on open-label correction phase Day 2 or Day 3, the site will contact IRT/RTSM to determine which on-site kit to use for the 28-day randomized treatment study phase. Thereafter, the 28-day randomized treatment study phase kits will be assigned weekly through IRT/RTSM and be dispensed by designated and trained site pharmacy staff. Study drug will be taken orally in the morning during the 28-day randomized treatment study phase, with or without food.

For doses administered in the clinic during both study phases, each dose will be individually dispensed by designated trained site staff.

Refer to Table 4 and Table 5 for dose titration and discontinuation criteria.

6.4.1 Investigational Products

Table 6 Investigational Products

Intervention Name	Sodium zirconium cyclosilicate (SZC)	Placebo
Dose Formulation/Unit Dose Strength	White to grey crystalline powder for oral suspension in 5 g and 10 g sachets	Powder for oral suspension in a sachet

Route of Administration	Oral	Oral
Use	Investigational product	Placebo comparator
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study treatment will be provided in sachet. Each sachet will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.	

6.5 Preparation/Handling/Storage/Accountability

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

Only participants enrolled in the study or their legally authorized representative may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.6 Measures to Minimize Bias: Randomization and Blinding

All participants achieving normokalemia during the open-label correction phase and entering the double-blind placebo-controlled phase will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the SoA (Table 1).

Returned study intervention should not be re-dispensed to the participants.

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator will document and report the action to AstraZeneca, without revealing the treatment given to participant 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 IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.7 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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

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

6.8 Concomitant Therapy

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

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

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

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

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

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

Table 7 Summary of Restricted Medications During Pre-study and/or Treatment Period

Type of Medication/Treatment	Timeline/Instructions
Renin–Angiotensin–Aldosterone System Inhibitor (RAASi) therapy	Patients cannot be started on RAASi therapy during the trial. For patients receiving RAASi at baseline: ACEi, ARB or ARNI: To be continued at the dose the patient was taking at baseline (Day 1). MRAs: Dose reductions from baseline permitted for MRAs
Sodium-glucose transport protein 2 inhibitor (SGLT2i) therapy	Patients receiving SGLT2i therapy at baseline will be allowed to continue stable dosing throughout the trial. Patients cannot be started on SGLT2i therapy during the trial.

Type of Medication/Treatment	Timeline/Instructions
Sodium bicarbonate or sodium citrate	Except if used as rescue therapy to treat metabolic acidosis (POCT bicarbonate <15 mmol/L) per investigator discretion (see Section 6.8.1).
Sodium polystyrene sulfonate (SPS), patiromer	Except if used as rescue to treat hyperkalemia according to medical judgment and if SZC/placebo has been discontinued.
K+ supplements or other drugs administered to raise sK+ (eg, K+ chloride)	Except if used to treat hypokalemia according to medical judgment.
Drugs with pH-dependent absorption	Drugs with pH-dependent absorption should be administered at least 2 hours before or 2 hours after SZC to mitigate the risk of drug interactions.

6.8.1 Rescue Therapy

Rescue therapy for hyperkalemia is defined as any therapeutic intervention considered necessary in accordance to local practice patterns to reduce sK+ in the setting of severe hyperkalemia (>6 mmol/L). This includes insulin/glucose, beta adrenergic agonists, calcium gluconate, sodium bicarbonate, and any dialysis or other forms of renal replacement treatments given with the goal of controlling the hyperkalemia.

Rescue therapy for low bicarbonate (<15 mmol/L) will be according to standard of care, such as use of sodium bicarbonate.

In order to be considered confirmed for meeting the rescue criteria, the POCT K+ or bicarbonate measurement must be repeated after a ≥10-minute interval, with both measurements meeting the cut-off value.

The patient will discontinue treatment and be discontinued from study drug following rescue. Rescue will be counted as an endpoint event with applicable end of study assessments, and proper documentation of the type of rescue will be recorded.

6.9 Dose Modification

All randomized patients start on 10 g QD, then titrate from there based on POCT K+. See Table 4 for dose titration.

6.10 Intervention After the End of the Study

Poststudy access to study treatment is not applicable. Patients are to be managed as per standard of care after study completion.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

To minimize risk for events related to severe hypokalemia, the following discontinuation criterion will be followed:

- Confirmed POCT K+ <3.0 mmol/L by taking a second measurement after a ≥10-minute interval, at any time during the study, the patient should immediately receive appropriate medical intervention and study drug should be permanently discontinued.

To minimize risk for events related to severe hyperkalemia, the following discontinuation criterion will be followed:

- Confirmed POCT K+ >6.0 mmol/L by taking a second measurement after a ≥10-minute interval, at any time during the study, the patient should immediately receive appropriate medical intervention and study drug should be permanently discontinued.

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

- If an absolute QTc >550 ms, or an increase in QTc interval >60 ms from baseline to more than 500 ms is reached, the patient should immediately receive appropriate medical intervention and be permanently discontinued from the study drug treatment. The QTcF algorithm is recommended. All patients meeting the QTc >500 ms criterion should immediately have K+ assessed, if not already done within 1 hour of performing the electrocardiogram (ECG).

For serious arrhythmia (eg, associated with POCT K+ <3.5 mmol/L or >5.6 mmol/L), study drug should be permanently discontinued.

To minimize risk for events related to severe metabolic acidosis, the following discontinuation

criterion will be followed:

- Confirmed POCT bicarbonate ≤15 mmol/L by taking a second measurement after a ≥10-minute interval, at any time during the study, the patient should immediately receive appropriate medical intervention and study drug should be discontinued.

For discontinuation pertaining to COVID-19, please see Appendix E.

7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, home visit, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (Table 1). See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

The participant will discontinue the study intervention and be withdrawn from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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

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

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

For management of study procedures during the COVID-19 pandemic, please see Appendix E.

At screening, some of the variables that will be collected will include demographics (eg, age, gender, race, ethnicity), a comprehensive medical and surgical history (eg, presence of diabetes mellitus type 1 or 2, HF, hypertension, CKD, prior history of hyperkalemia), baseline laboratory results (see Table 8). For measurement of K+ and bicarbonate, POCT K+ and POCT bicarbonate will be utilized for study inclusion criteria, eligibility for the randomized placebo-controlled phase and for titration of SZC/placebo. Central laboratory sK+ and POCT bicarbonate will be utilized for study assessments.

8.1 Efficacy Assessments

8.1.1 Potassium

Whole blood samples will be analyzed locally using POCT devices to generate K+ for the purposes of study inclusion, dose adjustments, and monitoring. Samples drawn at the same timepoints will be prepared and shipped to the central laboratory for analysis of sK+. All serum samples should be examined and any hemolyzed samples must be redrawn. In the event that hemolysis or other artifacts are suspected based on the reported POCT K+ result, the blood samples must be re-drawn to confirm the result. Only the confirmatory sample result needs to be reported in the eCRF. The primary endpoint will use the central laboratory sK+ measurement from Visit 7 if available. If Visit 7 central laboratory sK+ is missing, then Visit 6 central laboratory sK+ will be used in its place under the principle of last observation carried

forward (LOCF). If central laboratory sK+ is missing for Visits 6 and 7, then sK+ will be replaced by POCT values adjusted to reflect the mean difference between POCT and sK+ values from all available paired laboratory samples. (Visit 7 POCT will be used unless missing, in which case Visit 6 POCT will be used).

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

8.1.2 Bicarbonate

As bicarbonate measurement levels can decrease with exposure to the air, this study will utilize POCT to measure bicarbonate instead of central laboratory serum bicarbonate to improve accuracy.[18] The POCT measurement will be used to determine inclusion of patients in the study and in determining endpoints related to bicarbonate. The POCT blood analyzers along with the appropriate chemistry panels measure TCO2 which includes CO2 in several states: CO2 in physical solution and loosely bound to proteins, bicarbonate (HCO3-), carbonate (CO3) anions, and carbonic acid (H2CO3).[19] The serum bicarbonate measured by most central laboratories is actually the TCO2; thus, the POCT bicarbonate measurement is equivalent to measuring the serum bicarbonate reported by central laboratories.

8.1.3 Chloride

Serum chloride will be measured as part of the clinical safety laboratory assessments for Visits 1, 3, 7, and 8.

8.1.4 Urine Analysis

When possible, the first morning void spot urine will be collected at the timepoints indicated in the SoA (Table 1). Urinary albumin, ammonium, citrate, pH, and creatinine will be measured at the central laboratory and reported. Urine anion gap will be calculated based on sodium, potassium, and chloride ions. Albumin-to-creatinine-ratio (UACR), which will be calculated based on the measured urinary albumin and creatinine, will be reported. Ammonium-to-creatinine ratio will be calculated based on the measured urinary ammonium and creatinine and reported.

8.2 Safety Assessments

Safety will be assessed throughout the study. A complete baseline profile of each patient will be established through demographics, medical history, clinical laboratory values, vital signs, and physical assessments. During the course of the study, vital signs, ECG, and laboratory tests will be performed as specified in the SoA (Table 1). Adverse events (AEs), SAEs, and ongoing concomitant medication usage will be monitored and recorded throughout the study. Serious adverse event reports will be evaluated individually to assess the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. All AEs will be followed until resolved, stable or until the

patient's end of study visit. See Section 8.3 for details on AE and SAE reporting.

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

8.2.1 Physical Examinations

A complete physical examination will be performed at screening (Visit 1) and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. Body weight and height will be measured at the screening visit. Weight will be measured as specified in the SoA. Patients should be in light indoor clothes without shoes.

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

8.2.2 Vital Signs

The vital signs include tympanic temperature, systolic and diastolic BP, pulse rate and respiratory rate and will be assessed as outlined in the SoA (Table 1). Blood pressure and pulse rate should be measured with a completely automated device in triplicate with at least 1-minute intervals between measurements after being comfortably at rest in a seated position with the back and feet supported (ie, by chair back and floor or platform, respectively) quietly for at least 5 minutes. Manual techniques will be used only if an automated device is not available. The position of the patient should be comfortable with the arm where the BP 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 patient will be instructed to relax as much as possible and to not talk during the measurement procedure. The same device should preferably be used for the patient during the course of the study and in the same arm. The first reading of the BP and pulse rate should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

Vital signs will be performed at the timepoints as specified in the SoA (Table 1).

8.2.3 Electrocardiograms

An ECG will be performed at screening, randomization, end of treatment, and follow-up (as specified in the SoA [Table 1]), and according to clinical judgment in connection with severe hypokalemia (sK+ <3.0 mmol/L), severe hyperkalemia (sK+ >6.0 mmol/L), or any symptoms or clinical events suggesting cardiac arrhythmia.

QTcF should be recorded at each ECG measurement.

The ECG data should be recorded in the eCRF, including QTcF, in connection with reporting AEs that concern arrhythmia.

For study patients with pacemakers:

- All ECG variables, including QT/QTcF, should be read manually and be recorded in the eCRF.
- If not fulfilling the inclusion/exclusion criteria or fulfilling the discontinuation criteria, pacemaker patients should be managed as recommended by protocol (without exceptions).

8.2.4 Clinical Safety Laboratory Assessments

Urinalysis and blood for the determination of clinical chemistry and hematology as well as urine pregnancy test, will be taken at the visits indicated in the SoA.

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

The following variables will be measured and analyzed.

Table 8 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum)
B-Hemoglobin (Hb)	S-Sodium (Na+)
B-Leukocyte count	S-Potassium (K+)
B-Leukocyte differential count (absolute count)	S-Bicarbonate (Total CO_2)
B-Platelet count	S-Chloride (Cl-)
B-Hematocrit (Hct)	S-Glucose
	S-Creatinine
	S-Blood Urea Nitrogen (BUN)
	Urea (BUN)/Creatinine Ratio
	eGFR using the CKD-EPI formula
Urinalysis (dipstick)	Anion gap (blood, from POCT or calculated based on POCT)
U-Hb/Erythrocytes/Blood	S-Albumin
U-Protein/Albumin	S-Total Protein
U-Glucose	S-Calcium (Ca++)
	S-Magnesium (Mg++)
	S-Phosphate (PO_4)
	S-Bilirubin, total
	S-Alkaline phosphatase (ALP)
	S-Alanine amino transferase (ALT)

	S-Aspartate amino transferase (AST)

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 the center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the start of the open-label correction phase throughout the treatment period and including the follow-up period.

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

If the investigator becomes aware of a SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

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

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)

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

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- SAE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant, reported in response to the open question from the study site staff, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or

symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

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

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

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

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

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

8.3.6 Reporting of Serious Adverse Events

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

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

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform

AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study site staff how to proceed. Investigators or other site personnel will send relevant eCRF modules by fax to the designated AstraZeneca representative.

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

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

8.3.7 Reporting of AEs/SAEs in Relation to COVID-19

All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP. For patients experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the COVID-19 virus is the infectious organism and the AE will be recorded accordingly. If a patient presents with clinical signs and symptoms suggestive of COVID-19, a test will be requested where possible:

- If the test is positive, record “COVID-19 positive” in the Adverse Event Field.
- If the test is negative, record “COVID-19 negative” in the Adverse Event Field, along with the AE/SAE signs and symptoms and/or other diagnosis.

If a test has not been performed or result is not available and signs and symptoms, as judged by the Investigator, are suggestive of COVID-19 infection, record “COVID-19 suspected” in the Adverse Event Field. If the investigator has other concurrent diagnoses for the patient’s signs and symptoms (eg, pneumonia), these will be recorded as separate AEs.

8.3.8 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.8.1 Maternal Exposure

Women of childbearing potential who are planning on becoming pregnant are not allowed to be included in this study. Should a pregnancy still occur, the IP should be discontinued immediately, and the pregnancy reported to AstraZeneca.

If a participant becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.8) and within 30 days for all other pregnancies.

The same timelines apply when the outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.8.2 Paternal Exposure

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

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until a time period of 12 weeks after last dose as indicated by previous studies (pre-clinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.9 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately

but no later than 24 hours of when he or she becomes aware of it.

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

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

8.4 Overdose

During the initial open-label correction phase, any SZC dose greater than 30 g within 1 day, or continuation of the correction dose (10 g TID) for more than 48 hours will be considered an overdose.

During the randomized maintenance period, a dose higher than 15 g per day 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 on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

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

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, see Appendix C.

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Immunogenicity will not be assessed in this study.

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

CCI [redacted] will be collected at screening.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum.

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection, shipment, and destruction of these samples can be found either in the appendices or in the laboratory manual.

For storage and destruction of genetic samples, see Appendix D.

8.8 Health Economics

Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The statistical hypotheses for the primary endpoint are:

Null: No difference in the Occurrence (yes/no) of patients having a normal sK+ on Day 29 (Visit 7) without need for rescue treatment for hyperkalemia at any point during the randomized phase between SZC and placebo.

Alternate: Difference in the occurrence of patients having a normal sK+ on Day 29 without need for rescue treatment for hyperkalemia at any point during the randomized phase.

Hypotheses for the secondary endpoints are provided in Section 9.4.3.2.

9.2 Sample Size Determination

- Prior data: Proportion of patients with serum bicarbonate between16-20 mmol/L inclusive who had a 3 mmol/L or greater increase in serum bicarbonate with SZC versus placebo from ZS-004,[20] Global Harmonize trial,[21] and ZS-005.[22]
- SZC: 92/235 = 0.39 achieved an increase in serum bicarbonate ≥3 mmol/L
- Placebo: 7/40 = 0.175 achieved an increase in serum bicarbonate ≥3 mmol/L
- Sample size estimate*
    - 20% absolute difference:
    - Alpha=0.05, Power=80%
    - Control=0.175 with serum bicarbonate increase of 3mmol/L or more
    - SZC=0.39 with serum bicarbonate increase of 3mmol/L or more
        - *Actual effect size = 0.215
    - N=68 per group (136).
    - N=148 (accounting for 8% drop-out from initial phase to randomized-withdrawal phase)

*Sample size would be smaller if based on primary endpoint of mean sK+ (N=18 per arm @90% power).

Approximately 477 patients will be screened. Approximately 148 patients will be enrolled to the open-label phase of the study to achieve 136 randomly assigned to study intervention.

9.3 Populations for Analyses

Table 9 Populations for Analysis

Analysis Set	Description
Full Analysis Set (FAS)	The primary analysis set for the primary, secondary, CCI will include patients who achieve normokalemia at the end of the open-label correction phase and enter the randomized placebo-controlled phase. Patients will be analyzed on an intent-to-treat basis according to their randomized investigational product (IP).
Safety Set Open (SSO)	All patients enrolled in the open-label correction phase who took at least 1 dose of study drug. Patients will be analyzed as a single group.
Safety Set Randomized (SSR)	All patients who achieve normokalemia at the end of the open-label correction phase and enter the randomized placebo-controlled phase. Patients will be analyzed according to the IP received.
Per Protocol Set (PPS)	FAS patients without any important protocol deviations leading to exclusion from the PPS. Patients will be analyzed according to their randomized IP.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

All data processing, summarization, and analyses will be performed using Version 9.3 (or later) of the SAS® statistical software package.

The SAP will detail any approach to be taken to control for multiplicity for the primary and secondary endpoints. The primary and secondary endpoints will present two-sided p-values in line with the study objectives and the corresponding significance level of the hypotheses will be reported alongside these p-values subject to the methods used to control for multiplicity.

Continuous data will be summarized by treatment group using the number of observations available (n), mean, standard deviation (SD), minimum, quartile 1, median, quartile 3 and maximum. Categorical data will be summarized by treatment group using the count of patients and percentage.

Screening baseline is defined as the last available assessment prior to the first dose of open-label treatment. Measurements made on the same date as the first dose of open-label treatment will not be considered unless the measurement is confirmed to be pre-dose by the times the measurement and dose are recorded. Randomization baseline is defined as the last available assessment prior to or on the date of the randomization visit for all patients, unless otherwise

specified.

Post-hoc analysis will be considered depending on study findings.

9.4.2 COVID-19 Considerations

COVID-19 is anticipated to have a minimal impact on this study due to the 36-day follow-up period and the analysis approaches outlined below for the primary and secondary endpoints. For the primary and secondary endpoints, a Visit 6 value for sK+ is used if a Visit 7 value is unavailable due to a missed visit or drop-out related to COVID-19 and an approach to use POCT values is also used.

Any other analytic strategies needed to assess and address issues pertaining to COVID-19 related to estimands, missing data, validity, and modifications of statistical analysis methods or need for additional analyses will be described in the SAP.

9.4.3 Efficacy

9.4.3.1 Primary Endpoint

The Occurrence (yes/no) of patients having normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) without rescue treatment for hyperkalemia at any point during the randomized phase in the SZC versus placebo arm.

Analysis Methods

The occurrence of patients having normal sK+ will be analyzed using a logistic regression analysis with response as the dependent variable and randomized treatment group as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS.

The following rules will be implemented to account for missing laboratory results:

a. If Visit 7 central laboratory sK+ is missing, then Visit 6 central laboratory sK+ will be used in its place (last observation carried forward [LOCF])
b. If central laboratory sK+ is missing for Visits 6 and 7, then sK+ will be replaced by POCT value adjusted to reflect the mean difference between POCT and sK+ values from all available paired laboratory samples. (Visit 7 POCT would be used unless missing in which case Visit 6 POCT will be used.)
c. If no results (central lab sK+ or POCT K) are available for Visit 6 and 7, then classify as non-evaluable.

A sensitivity analysis will be conducted which will include the following characteristics as independent variables in the logistic regression analysis: race, gender, age at baseline (<65,

≥65), CKD stage at baseline (3, 4, or 5) and diabetes status at baseline. Additional sensitivity analyses will also be carried out related to the proportion of patients achieving normokalemia in the SZC versus placebo arm. A sensitivity analysis will be conducted repeating the primary analysis but conducted in the PPS.

9.4.3.2 Secondary Endpoints

1 *Mean change in serum bicarbonate from baseline (Day 1) to Day 29 (Visit 7) in SZC versus placebo arm*

Hypotheses

Null: No difference in mean change in serum bicarbonate from baseline to Day 29 between SZC and placebo.

Alternate: Difference in mean change in serum bicarbonate from baseline to Day 29 between SZC and placebo.

Analysis Methods

The mean change in serum bicarbonate from baseline (Day 1) will be analyzed using analysis of covariance (ANCOVA) analyses at the significance level 5% (2-sided), with randomized treatment as main effect and baseline bicarbonate as covariate. For patients needing rescue treatment for low bicarbonate, the last value of POCT bicarbonate during the randomized period prior to rescue treatment will be analyzed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.

An additional sensitivity analysis will be carried out using another ANCOVA analysis that replaces missing POCT bicarbonate values with central laboratory serum bicarbonate values and includes a covariate in the model to control for central laboratory values.

2 *Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥2 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low bicarbonate in SZC versus placebo arm*

Hypotheses

Null: No difference in the occurrence of patients having an increase in serum bicarbonate of ≥2 mmol/L from baseline to Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo.

Alternate: Difference in the occurrence of patients having an increase in serum bicarbonate of ≥2mmol/L from baseline to Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo.

Analysis Methods

The occurrence of patients having an increase in serum bicarbonate of ≥2 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low bicarbonate will be analyzed using a logistic regression analysis with response as the dependent variable and randomized treatment group as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.

The following rules will be implemented for missing laboratory results:

a. If Visit 7 POCT bicarbonate data is missing, then Visit 6 POCT bicarbonate will be used in its place (LOCF).
b. If POCT bicarbonate is missing for Visits 6 and 7, then POCT will be replaced by central laboratory bicarbonate value adjusted to reflect the mean difference between POCT and central laboratory bicarbonate values from all available paired laboratory samples. (Visit 7 central laboratory bicarbonate will be used unless missing, in which case Visit 6 central laboratory bicarbonate will be used.)
c. If no results (POCT or central laboratory bicarbonate) are available for Visits 6 and 7, then classify as non-evaluable.

A sensitivity analysis will be conducted which will include the following characteristics as independent variables in the logistic regression analysis: race, gender, age at baseline (<65, ≥65), CKD stage at baseline (3, 4, or 5), and diabetes status at baseline.

3 *Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low bicarbonate in SZC versus placebo group*

Hypotheses

Null: No difference in the occurrence of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline to Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo.

Alternate: Difference in the occurrence of patients having an increase in serum bicarbonate of ≥3mmol/L from baseline to Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo.

Analysis Methods

The occurrence of patients having an increase in serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low bicarbonate will be analyzed using a logistic regression analysis with response as the dependent variable and randomized treatment group as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.

The rules for missing POCT bicarbonate implemented for the secondary endpoint #2 will also be implemented for this endpoint. Sensitivity analysis and subsequent subgroup analyses will be implemented as described for secondary endpoint #2.

4 *Occurrence (yes/no) of patients having a normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) and an increase in serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for hyperkalemia or low bicarbonate*

Hypotheses

Null: No difference in the occurrence (yes/no) of patients having normal sK+ (between 3.5 and 5.0 mmol/L inclusive) and an increase in serum bicarbonate of ≥3 mmol/L from baseline to Day 29 between SZC and placebo.

Alternate: Difference in the proportion of patients achieving normal sK+ (between 3.5 and 5.0 mmol/L inclusive) and an increase in POCT bicarbonate of ≥3 mmol/L from baseline to Day 29 between SZC and placebo.

Analysis Methods

The occurrence of patients having a normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) and a serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) without need for rescue treatment will be analyzed using a logistic regression analysis with response as the dependent variable and randomized treatment group as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.

The rules for missing K+ laboratory results for the primary endpoint and POCT bicarbonate for secondary endpoint #2 above will also be implemented for this endpoint. Sensitivity analysis and subsequent subgroup analyses will be implemented as described for secondary endpoint #2.

5 *Occurrence (yes/no) of patients having serum bicarbonate ≥22 mmol/L on Day 29 (Visit 7) without need for rescue treatment for low bicarbonate in SZC versus placebo group*

Hypotheses

Null: No difference in the occurrence of patients having serum bicarbonate ≥22 mmol/L at Day 29 from without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo.

Alternate: Difference in the occurrence of patients having serum bicarbonate ≥22 mmol/L at Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo.

Analysis Methods

The occurrence of patients with serum bicarbonate of ≥22 mmol/L at Day 29 (Visit 7) without need for rescue treatment for low bicarbonate will be analyzed using a logistic regression analysis with response as the dependent variable and randomized treatment group as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.

The rules for missing POCT bicarbonate implemented for the secondary endpoint #2 will also be implemented for this endpoint. Sensitivity analysis and subsequent subgroup analyses will be implemented as described for secondary endpoint #2.

6 *Occurrence (yes/no) of patients having a normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) and a serum bicarbonate of ≥22 mmol/L on Day 29 (Visit 7) without need for rescue treatment for low bicarbonate or hyperkalemia*

Hypotheses

Null: No difference in the occurrence of patients having normal sK+ (between 3.5 and 5.0 mmol/L inclusive) and serum bicarbonate of ≥22 mmol/L on Day 29 between SZC and placebo.

Alternate: Difference in the occurrence of patients having normal sK+ (between 3.5 and 5.0 mmol/L inclusive) and serum bicarbonate of ≥22 mmol/L from baseline to Day 29 between SZC and placebo.

Analysis Methods

The occurrence of patients having a normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) and serum bicarbonate of ≥22 mmol/L on Day 29 (Visit 7) without need for rescue treatment will be analyzed using a logistic regression analysis with response as the

dependent variable and randomized treatment group as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.

The rules for missing K+ laboratory results for the primary endpoint and POCT bicarbonate for secondary endpoint #2 above will also be implemented for this endpoint. Sensitivity analysis and subsequent subgroup analyses will be implemented as described for secondary endpoint #2.

7 *Occurrence (yes/no) of patients needing rescue treatment for low bicarbonate (POCT ≤15 mmol/L) during the randomized phase between SZC and placebo.*

Hypotheses

Null: No difference in the occurrence of patients needing rescue treatment for low bicarbonate during the randomized phase between SZC and placebo.

Alternate: Difference in the occurrence of patients needing rescue treatment for low bicarbonate during the randomized phase between SZC and placebo.

Analysis Methods

The occurrence of patients needing rescue treatment for low bicarbonate will be analyzed using a logistic regression analysis with rescue treatment as the dependent variable and randomized treatment as the independent variable. The odds ratio along with the 95% confidence intervals and two-tailed p-value (significance declared <0.05) will be displayed. The analysis will be based on the FAS. A sensitivity analysis will be conducted based on the PPS.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9.4.4 Safety

Safety will be assessed in terms of AEs, SAEs, AEs leading to treatment discontinuation, laboratory data, vital signs, ECG, and full physical examinations during the open-label phase, the randomized phase, and through to follow-up. These assessments will be collected for all patients.

Appropriate summaries of these data will be presented by treatment group. The AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system of nomenclature system organ class (SOC) and preferred term (PT).

A treatment emergent AE (TEAE) will be defined as an AE with the start date on or after the first dose date and up to (and including) 7 days after the last dose date. Similarly, the number of patients experiencing SAEs, AEs that led to withdrawal, AEs that led to death and treatment related AEs, and number of such events, will be summarized by treatment group.

An overview of edema-related AEs and instances of sK+ <3.5 will be presented.

The identified risk of hypokalemia is defined by laboratory values and not by specific MedDRA terms.

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

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

All safety analyses will be performed on the Safety Sets. In general, safety assessments will be reported descriptively by treatment group and separately for the open-label and randomized-withdrawal phases. Full details on safety analyses will be provided in the SAP.

9.5 Interim Analyses

An informal interim analysis for the purpose of Sample Size Re-estimation (SSR) will be conducted when approximately 68 person-months of follow-up time of the total 136 person-months have occurred (an information time of 0.5) to adjust for potential deviations from the pre-specified expected effect sizes based on updated knowledge provided by the observed effect sizes which inform the key secondary efficacy endpoint (occurrence of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to Day 29 without need for rescue treatment for metabolic acidosis). This analysis will estimate the true effect size and

re-estimate the additional number of subjects that need to be accrued to achieve sufficient power based on this new information. Enrolment may be extended to accrue this number of additional subjects if it is determined this can be achieved in a cost-effective manner. The analysis will be unblinded to the party who executes it but blinded to the study team. The complete details of the SSR will be described in the SAP.

9.6 Data Monitoring Committee

No Data Monitoring Committee is planned for this study. Study is on-label for an approved drug.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB and other relevant documents (eg, 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 and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of 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.
    - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized 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 center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any

time and for any reason during the retention period.

A 4 Data Protection

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

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety function at AstraZeneca. Issues identified will be addressed, for example, by amending the CSP and letters to Investigators.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-

compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

Reasons for the early closure of a study site by the sponsor or investigator may include but are

not limited to:

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

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

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

Life-threatening

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

Hospitalization

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

Important medical event or medical treatment

Medical and scientific judgment 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, hospitalization, disability or incapacity but may jeopardize the participant 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 judgment 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 (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology 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 no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

B 4 Medication Error

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

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 recognized that could have led to an error.

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

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives 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.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

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, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

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

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA (ie, the entire genome).
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
    - Previous allogeneic bone marrow transplant
    - Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection
    - Healthy Volunteers and pediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2.

Collection of Samples for Genetic Research

The blood sample for this genetic research will be obtained from the participants at Visit 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

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

Management described in this appendix related to study visits and SARS-COV-2 testing should be implemented only during the COVID-19 pandemic and will apply until further notice, as communicated by the sponsor. Changes to study visits due to participants not wishing to or being unable to visit sites should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

Changes that may affect the study participants' participation in the study should be communicated to the participant. It is the investigator's responsibility to inform the study participants of any change in the study conduct that may be implemented. The participants' assent and/or consent to any such change in study conduct should also be documented.

E 2 Risk Assessment for COVID-19 Pandemic

SZC is a K+ binder acting in the GI tract and is not absorbed. No additional risk from COVID-19 is expected due to SZC. However, the risk of exposure to infected people cannot be completely excluded during study participation as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff).

Measures to mitigate the risks associated with COVID-19

- This study will start or resume enrolment only when the sponsor and investigator deem it is appropriate. In addition, the enrolment at a site level will only start or resume when local regulations and guidelines allow.
- National laws and local recommendations for regarding the pandemic will be strictly adhered to.
- The site is encouraged to contact the participant within 1 day prior to a study visit, see next section. Study visits may be modified where appropriate and permitted by local practice, see Section E 4.

E 3 COVID-19 Assessment

In order to limit potential infection at the site, the site is recommended to contact the participant within 1 day prior to any study visit to ask for signs and symptoms related to COVID-19. COVID-19 symptoms include, but are not limited to: fever or chills, cough,

shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhea.

Recommended questions to determine risk of COVID-19 are included below for information:

1 Have you experienced unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and/or new loss of taste or smell within the past 14 days?
2 Have you been in contact with anyone who is sick with or exhibiting Covid-19 symptoms in the last 14 days?
3 Have you been in contact in the last 14 days to someone who was diagnosed with Covid-19 within 14 days from your contact?

COVID-19 prior to screening

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

Suspected COVID-19 after screening

Participant is severely ill or hospitalized:

- If the participant becomes symptomatic after screening, and has suspected COVID-19 (regardless of any SARS-Cov-2 test results that may be available), and is severely ill and/or hospitalized, IP will be permanently discontinued.
- If possible, the participant is encouraged to attend the study visits according to schedule even if off treatment. Visits may be modified per guidance in Section E 4 and per local regulations and guidelines related to COVID-19.

Participant is NOT severely ill or hospitalized:

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

Regardless if IP is continued or not, the participant can attend the study visits according to schedule IF the investigator discerns ability of participant or in accordance to institution policy keeping in mind social distancing and potential exposure to other people. Visits may be

modified per guidance in Section E 4 and per local regulations and guidelines related to COVID-19. See Modified Visits below.

E 4 Modified Visits

As a general rule, the sponsor's expectation is that as long as conditions permit, the participant should remain in the study and complete visits as per the schedule. Of note, when directly interacting with a participant within the boundaries set by this guidance document (eg, study visit of any kind) it is expected and assumed by the sponsor that it is done in accordance with 'social distancing' and protection requirements as set by local orders to manage the COVID-19 pandemic. The specifics of such conduct are not part of the scope of this document.

Visits may be modified if needed due to the COVID-19 pandemic, if an on-site visit is not possible due to participants not wishing to or being unable to visit sites. Modified visits can only replace a site visit if allowed by local/regional guidelines and regulations.

The sponsor should be notified of any deviation from the regular scheduled visits and planned study procedures, and of the alternative plan the site will implement. Any deviation from the protocol should be documented in the participant file with a comment explaining the relation to COVID-19. A modified visit may for example be a home visit. Regardless of the modified visit approach, every effort should be made to complete the full scope of the study visit activities and procedures (see the SoA, Table 1). If this is not possible, the minimum safety measurements should always include sK+ measurements and, where indicated, an ECG, in addition to collection of AEs and concomitant medication.

If an in-person visit with the participant is not possible, the site may consider having a telemedicine visit. The term telemedicine visit refers to remote contact with the participants using telecommunications technology such as phone calls, virtual or video visits, and mobile health devices. Having a telemedicine contact with the participant will allow AEs, and concomitant medication to be reported and documented. At the earliest possibility, the minimum safety measurements including sK+ measurements and, where indicated, an ECG must be done.

Appendix F Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ACEi	angiotensin-converting enzyme inhibitor
ADR	adverse drug reaction
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
ARNi	angiotensin receptor-Neprilysin inhibitor
BP	blood pressure
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPS	calcium polystyrene sulfonate
CSP	Clinical Study Protocol
CV	cardiovascular
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HF	heart failure
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT/RTSM	Interactive Response Technology/Randomization and Trial Supply Management
K+	potassium
MedDRA	Medical Dictionary for Regulatory Activities
MRA	mineralocorticoid receptor antagonist
NK	normokalemia or normokalemic

Abbreviation or special term	Explanation
POCT	Point of Care Test
PPS	Per Protocol Set
QD	once daily
QOD	every other day
QTcF	QT interval corrected by the Fridericia method
RAASi	renin-angiotensin-aldosterone system inhibitor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGLT2i	sodium-glucose transport protein 2 inhibitor
sK+	serum potassium
SMQ	standardized MedDRA queries
SoA	Schedule of Activities
SOC	Standard of Care
SPS	sodium polystyrene sulfonate
SSO	Safety Set Open
SSR	Safety Set Randomized
SZC	sodium zirconium cyclosilicate
TID	three times daily
UACR	urine albumin-to-creatinine ratio
US	United States

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