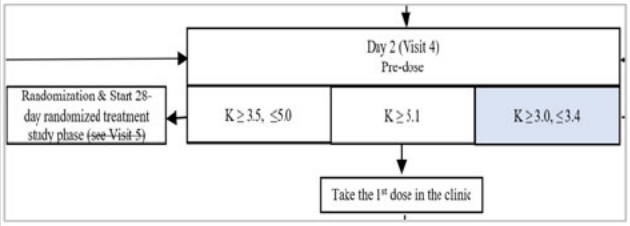
Clinical Study Protocol	
Drug Substance	ZS
Study Code	D9480C00001
Version	6.0
Date	19 August 2020

A phase 3 multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (sodium zirconium cyclosilicate), in patients with hyperkalemia-HARMONIZE Asia

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 6.0, 19 August 2020		
The main reason for the Clinical Study Protocol (CSP) Version 6.0 was to exclude India from the participating countries due to the COVID-19 pandemic and as a consequence reduce the overall study sample size. The current China sample size remains unchanged and can still provide sufficient statistical power to support the safety and efficacy analysis of the study. Additional changes made to the CSP include some minor improvements. Detailed changes are summarized below:		
Section	**Description of Change**	**Rationale of Change**
Clinical Study Protocol Synopsis – Study site(s) and number of patients planned	Updated the following information: This study will be conducted in approximately ~~45~~ 35 centers in China ~~and India~~. Before patients are randomized to the double-blind phase, they will receive open-label ZS for 24 or 48 hours during the initial phase. It is expected that approximately ~~555~~ 490 patients will need to be enrolled, to have approximately ~~337~~ 280 patients entered into the open-label initial phase resulting in ~~320~~250 patients being randomized in the 28-day randomized treatment study phase. Enrolment will be stopped when ~~320~~250 patients have been initiated with the 28-day randomized treatment study phase.	Updated the summary to reflect the updated information about the participating country, study sites and planned patients for the study.
Clinical Study Protocol Synopsis – Statistical Methods	Updated the following information: Assuming an inter-subject standard deviation of 0.50, approximately ~~320~~250 patients, (~~128~~100 patients per active dose treatment arm and ~~64~~50 patients for placebo control arm), will provide ~~>95~~ >90% power to detect a mean difference of 0.30 in mean 28-day randomized treatment phase Day ~~8-29 difference~~ 8-29, comparing each active dose (high to low) vs. placebo control using a two-sided t-test at a significance level of 5%. Assuming ~~95~~90% of patients will be normokalemic after treatment in the open label initial phase ~~with at least 1 dose of ZS 10g~~ (see Section 7.2), approximately ~~337~~ 280	Updated the summary to reflect the statistical information for the revised number of planned patients for the study.

	patients will be needed to enter the open-label initial phase.	
Section 4 – Figure 4 Flow chart based on the Potassium level, which will be measured by i-STAT	Updated the details across the figure to reflect the that whole blood Potassium (K) is being tested for i-STAT measurement instead of Serum Potassium (S-K). Updated the details for Day 2 (Visit 4):  	Updated to clarify that the i-STAT measurement is using whole blood rather than serum. To correct the typographical error for the Visit 5 label in the figure.
Section 4.3.2 to Section 4.3.3 Open-label initial phase Day 2 (Visit 4) and Randomization Visit – For patients not entering the 28-day randomized treatment study phase	Updated the following information across the section that the patient will bring the used and/or unused IP and completed dosing schedule card with them.	Updated the applicable sentences in the section to clarify that the patients need to bring both the used and/or unused IP, and completed dosing schedule card for IP accountability.
Section 4.3.4 Randomization Visit – For patients entering the 28-day randomized treatment study phase	Updated the following information: They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day and to bring the used and/or unused IP and completed dosing schedule card with them when they return to the clinic.	Updated to clarify that the patients need to bring both the used and/or unused IP, and completed dosing schedule card for IP accountability.

Section 4.3.5 to Section 4.3.13 28-day randomized treatment study phase Day 2–Day 29 (Visit 6 – Visit 14)	Updated the following information across the section that the patient will bring the used and/or unused IP and completed dosing schedule card with them.	Updated the applicable sentences in the section to clarify that the patients need to bring both the used and/or unused IP and completed dosing schedule card for IP accountability.
Section 8.2 Sample Size Estimate	Updated the following information: The sample size is determined to detect a clinically meaningful difference in the primary endpoint of the mean S-K during the 28-day randomized treatment study phase Study Days 8-29 between each active dose (high to low) vs. placebo control. Assuming an inter-subject standard deviation of 0.50, approximately ~~320~~250 patients, (~~128~~100 patients per active dose treatment arm and ~~64~~50 patients for placebo control arm), will provide ~~>95~~>90% power to detect a mean difference of 0.30 in mean S-K during Study Days 8-29, comparing each active dose (high to low) vs. placebo control using a two-sided t-test at a significance level of 5%. Assuming ~~95~~90% of patients will be normokalemic after treatment in the open label initial phase ~~with at least 1 dose of ZS 10g~~ (see Section 7.2), approximately ~~337~~280 patients will be needed to enter the open-label initial phase. The power and sample size is determine based on the number of patients required to evaluate the primary hypothesis of the study. However, in the testing sequence presented in Table 6, the open-label initial phase mean change from baseline of S-K 48 hours after first dose of ZS 10g will be evaluated first. A sample size of ~~320~~280 patients will provide >99% power to detect a more than 18% relative reduction (i.e., 1.05 absolute reduction) in mean change from	Updated to reflect the statistical considerations for the revised number of planned patients for the study.

	baseline of S-K 48 hours after the first dose of ZS 10g during the open-label treatment initial phase.	
Section 8.5.4 Analysis in subsets of patients	Deleted the paragraph in this section: ~~To facilitate a benefit risk assessment for the purpose of regulatory submission in China and India, subpopulation of patients from these countries will be analyzed separately, with respect to efficacy and safety variables, for both phases of the study. More details on these analyses will be presented in the SAP.~~	Sub-group analysis is no longer applicable since only a single country is participating in the study.

Version 5.0, 19 June 2020	
The main reasons for the Clinical Study Protocol (CSP) Version 5.0 were to update the duration of initial treatment phase from 48 hours to 24 or 48 hours (depending on potassium value), to allow subjects who achieve normokalemia after 24-hour treatment to be randomized earlier; update the exclusion criteria to address potential risk of patients with arrhythmia/pro- arrhythmia conditions, revise ECG recording description to be consistent across the CSP, and add some guidance for COVID-19. Additional changes made to the CSP include some minor improvements. The detailed changes are summarized below:	
Sections	**Summary & Rationale of Changes**
ALL applicable sections	"48-hour open-label initial phase" has been updated to "Open-Label Initial phase" across all sections in the CSP to accurately reflect the update of this treatment phase.
Clinical Study Protocol Synopsis	Updated the information to the changes outlined in applicable sections.
Section 1.1 Background and rationale for conducting this study	Updated and simplified background information on the clinical studies for ZS based on the latest Investigators Brochure version 9.0.
Section 1.2 Rationale for study design, doses and control groups	Updated information on the study rationale as a post-approval commitment study for China.
Section 1.3.2 Clinical Risks	Updated Clinical Risk information on the ZS based on the latest Investigators Brochure version 9.0.

Section 1.3.3 Clinical benefit-risk balance	Updated information about the known and expected benefits and risks and reasonably expected adverse events of ZS based on the latest Investigators Brochure version 9.0.
Section 1.4 Study Design	Updated the study design figure and the number of study visits to 14-15 visits which reflects the updated Open-Label Initiation Phase. Depending on the potassium value, patients can be randomized after achieving normokalemia after 24 or 48 hours of receiving open label ZS.
Section 1.4 – Figure 3 Study flow chart	Updated the study design figure and the number of study visits to 14-15 visits which reflects the updated Open-Label Initiation Phase.
Section 2.2 Secondary objectives	Updated information to reflect the Open-Label Initial Phase across the study objectives and clarify further the definition of secondary outcome measures.
Section 3.2 Exclusion Criteria	Exclusion criteria # 13-16 was added to exclude patients with history of QT prolongation, Congenital long QT syndrome, etc. as there is a risk that ZS can further prolong QT and could put patients at risk of proarrhythmic/arrhythmic condition.
Section 3.7 Methods for unblinding	Updated to clarify that only Investigators will have access to the unblinding procedure in IWRS/IVRS in case of unblinding situation.
Section 3.9 Discontinuation of Investigational Product	Clarified that the QTc(f) algorithm (QT interval corrected by the Fridericia method) is recommended for QTc calculation. Clarified the End of Study (EOS) scheduling between the 28-day randomized treatment phase and open-label initiation phase.
Section 3.10 Criteria for Withdrawal	Deleted paragraph about IP treatment withdrawal and clarified further in section 3.9.
Section 4 (Table 1): Study Plan detailing the procedures: optional Pre-screening, screening and open-label initial phase	Updated the table and footnote to reflect the changes for the Open-Label Initial Phase and Eligibility Criteria assessment at Randomization Visit for consistency with Table 2.

Section 4 (Table 2): Study Plan detailing the procedures: 28-day randomized treatment study phase	Updated the table to accurately reflect the visit name of Randomization Visit for the 28-day randomized treatment study phase.
Section 4.3.2 Open-label initial phase Day 2 (Visit 4)	Updated the section to reflect the changes for the Open-Label Initial Phase and further guidance on site actions relating to the patient's i-STAT potassium values during the Open-Label Initial phase.
Section 4.3.3 Randomization Visit - For patients not entering the 28-day randomized treatment study phase	Updated the section name to provide guidance on site actions for patients who will not enter the 28-day randomized treatment study phase at the end of the Open-Label Initial phase.
Section 4.3.4 Randomization Visit - For patients entering the 28-day randomized treatment study phase	Additional clarifications on the randomization procedure for patients who achieve i-STAT potassium values between 3.5 – 5.0 mmol/L, inclusive after 24 hours or 48 hours during the open-label initial phase.
Section 4 - Figure 4 Flow chart based on the S-K level, which will be measured by i-STAT	Updated the Flow chart to clarify the site actions based on the i-STAT potassium levels of the patient.
Section 5.2.1 Laboratory Safety Assessments	Updated to clarify that sample tubes and sample sizes will not vary since all materials will be provided by a central laboratory.
Section 5.2.1 – Table 3 Laboratory Safety Variables	Included S-Aldosterone in the sample collection guidelines requiring patients to be either standing or seated upright for at least 2 hours before sample collection. Clarified that all patients must be on fasting when collecting blood chemistry & hematology at Day 1 of Open-Label Initial Phase.
Section 5.2.3 ECG	Deleted the previous typographical error on subsection 5.2.3.1 28-day randomized treatment study phase Day 29 (Visit 14). Description for ECG recording was updated to be consistent with the content in Section 4.3.1. Additional guidance for ECG data collection for patients with pacemakers.

Section 5.2.4 Vital Signs	Updated that blood pressure should be checked in both arms at visit 3 to be consistent with Table 1.
Section 5.10 Volume of Blood	Updated the information to clarify subjects who achieve normokalemia after 24-hour treatment can be randomized earlier. Updated Table 5 to accurately reflect the visit name of Randomization Visit.
Section 5.11 Guidance related to assessments, and procedures during COVID-19 pandemic	Added new section to provide guidance on study assessments and procedures during the COVID-19 pandemic.
Section 6.2 Definitions of Serious Adverse Event	Added additional SAE reporting requirement includes reporting of malignant tumors during study conduct.
Section 6.5 Overdose	Added additional clarification on the definition of the ZS overdose during the study.
Section 7.2 Dose and Treatment Regimen	Updated the section to reflect the changes for the Open-Label Initial Phase and further guidance on site actions relating to the patient's i-STAT potassium values during the Open-Label Initial phase.
Section 8.1 Statistical Considerations	Clarified that Statistical Analysis Plan will be finalized prior to Database Lock.
Section 8.3.1 Full analysis sets (FAS)	Corrected the typographical error in the acronym FAS-RPT to "FAS-RTP".
Section 8.4.2 Secondary efficacy variables	Updated information to reflect the Open-Label Initial Phase in the secondary efficacy variables and clarify further the definition of secondary outcome measures. Updated the typographical error of the efficacy endpoint: Exponential (instead of Expected) rate of Change in S-K levels.
Section 8.5 Methods for statistical analyses	Removed paragraph of "Definitions of Baseline" as the information will be detailed in the Statistical Analysis Plan (SAP).
Section 8.5.3 Safety Analysis	Updated information on the definition of safety variables for analysis of Adverse Event and added clarifications on the analysis of hypokalemia.

Section 9.3 Study timetable and end of study	Updated the section to reflect the latest study timelines.
Section 10 Regulatory, Ethical and Study Oversight requirements	Updated the section to Regulatory, Ethical and Study Oversight requirements and added description on the following sub-sections: (10.2) Patient Data Protection, (10.3) Ethics and Regulatory Review – added Regulatory Reporting Requirement for SAEs, (10.6) Data Quality Assurance (previously Audits and Inspections), (10.7) Dissemination of Clinical Study, (10.8) Source Data, (10.9) Study and Site Start and Closure.
Appendix B: Handling of Human Biological Samples	Updated IATA 6.2 Guidance document to Handling of Human Biological Samples.
Appendix C: Guidance related to assessments, and procedures during COVID-19 pandemic	Additional information added to provide detailed guidance on study assessments and procedures during the COVID-19 pandemic.

Version 4.0, 23 December 2017
The main reasons for the Clinical Study Protocol Version 4.0 were to update the blood volume to align with the Central Laboratory requirement. Additional changes made to the protocol include multiple minor improvements. The main changes are summarized below.
Section 4 (Table 1): In Table 1 (Study plan and timing of procedures for the optional Pre-screening, screening and 48-hour open-label initial phase), the footnote marks were updated for minor improvements. Section 4 (Table 2): In Table 2 (Study Plan detailing the procedures: 28-day randomized treatment study phase), the table text was updated to improve the wording.
Section 5.10 (Volume of blood): In Table 4 and 5, blood volumes were updated to align with the Central Laboratory requirement.

Version 3.0, 20 October 2017
The main reasons for the Clinical Study Protocol Version 3.0 were to add the optional Pre-screening visit in order to support the patient recruitment and the monitoring for ECG was enhanced to align with the recommendation from CFDA. Changes were made to clarify guidance with respect to concomitant use of ZS and drugs with gastric pH-dependent bioavailability. Additional changes made to the protocol include multiple minor improvements. The main changes are summarized below.
Study Synopsis: The synopsis was updated to align with the amendments made in the body of the CSP.
Section 1.4 (Study Design): Figure 3 was updated to add the optional Pre-screening visit.
Section 3.1 (Inclusion criteria): The inclusion criteria for Pre-screening part and Screening part of the study were clarified. Section 3.2 (Exclusion criteria): The exclusion criteria for Pre-screening part and Screening part of the study were clarified. Section 3.3 (Patient enrolment and randomization): The two-stage informed consent process were introduced. The consented (optional Pre-screening consent) patients, who are eligible for participating the study, will subsequently be offered the option for consenting to the screening part of the study. Section 3.8 (Restrictions): The wording was improved. Section 3.9 (Discontinuation of investigational product): The discontinuation criteria for significant increase in PR interval was updated to better reflect that "new onset peak T-wave".
Section 4 (Table 1): The study plan and timing of procedures for the optional Pre-screening, screening and 48-hour open-label initial phase (Table 1) was updated as the optional Pre-screening visit was added. The footnote was added to clarify that blood potassium will be measured only by i-STAT at the optional Pre-screening visit. Patients who meet all Pre-screening criteria will be entered into the screening part of the study within 7 days. AE and SAE collection were clarified in the footnote. The wider visit window is defined in Table 1, is to be used if a scheduled visits could not be accomplished as pre-specified visit schedules, due to prolonged public holiday. Throughout section 4, minor typographical errors and formatting was updated to improve the wording. Section 4.1 (optional Pre-screening period (Visit 1)): The study procedures for the optional Pre-screening visit was added. Section 4.3.2 (48-hour open-label initial phase Day 2 (Visit 4)): ECG was added on Day 2 (Visit 4) to ensure the ECG monitoring and the serum potassium detection to be conducted simultaneously. Section 4.3.3 (48-hour open-label initial phase Day 3 (Visit 5)): The section was updated to emphasize that the study procedures to be performed if the i-STAT potassium value is > 5.0 mmol/L or < 3.5 mmol/L.

Section 4.3 (Follow-up period (EOS)): A note was added to clarify the wider visit window for the EOS visit, if the EOS falls on a prolonged public holidays.
Section 5.2.1 (Laboratory safety assessments): Table 3 was updated to clarify blood potassium would be measured only by i-STAT at the optional Pre-screening visit. A footnote was added to provide instruction that patients need to be either standing or seated upright for at least 2 hours before sample collection for P-Renin assessment. Section 5.2.3.1 (Resting 12-lead ECG): The section was updated to emphasize that patients developed severe hypokalemia (i-STAT potassium values <3.0 mmol/L) at any time during the study or > 6.2 mmol/L during the 28-day randomized treatment study phase, an additional ECG will need to be performed in order to enhance the ECG monitoring. Section 5.10 (Volume of blood): In Table 4, blood volume was updated and a footnote was added for blood potassium measurement at the optional Pre-screening visit. In Table 4 and Table 5, the blood volume required for blood potassium measurement by i-STAT was reduced and the blood volume required for clinical chemistry was increased, which were align with the Central Laboratory requirement.
Section 6.3.1 (Time period for collection of adverse events): The section was added to clarify that Adverse Events (including SAEs) will be collected from the time of main study informed consent, throughout the treatment period and including the EOS visit. SAEs will be collected from the time of the optional Pre-screening informed consent, throughout the treatment period and including the EOS visit.
Section 7.7.1 (Oral medications with gastric pH-dependent bioavailability): The section was added to clarify guidance with respect to concomitant use of ZS and drugs with gastric pH-dependent bioavailability. For a specific list of drugs the recommendation is to administer those at least 2 hours before or 2 hours after ZS to mitigate the risk of drug interactions.
Section 8.4.2 (Secondary efficacy variables): The section was updated for minor changes. Section 8.5 (Methods for statistical analyses): In the section of "Multiple testing strategy", wordings were modified.

Version 2.0, 03 March 2017
The main reasons for the Clinical Study Protocol Version 2.0 were to clarify how patients developing hypokalemia during the 48-hour open-label initial phase are to be monitored and handled, and to update the Benefit Risk section with additional information. Additional changes made to the protocol include multiple minor improvements. The main changes are summarized below.
Study Synopsis: The synopsis was updated to align with the amendments made in the body of the CSP.

Section 1.1 (Background and rationale for conducting this study): This section was updated to better reflect how hyperkalemia is treated. Minor typographical errors and formatting was updated. Section 1.2 (Rationale for study design, doses and control groups): This section was updated to better reflect the rationale for the study design and the doses selected. Minor typographical errors and formatting was updated in this section. Section 1.3 (Benefit/risk and ethical assessment): This section was updated to better reflect the benefits, risks, and benefit-risk balance of the study.
Section 2 (Study objective): Minor typographical errors and formatting was updated in this section. In particular, physical examination was added to "Outcome Measures" under the "Safety Objective" to ensure all collected data relevant to patient safety are thoroughly analyzed.
Section 3.2 (Exclusion criteria): The wording in exclusion criterion 3 was improved. Exclusion 15 was added to clarify that the study is in outpatients. Section 3.6 (Methods for ensuring blinding): This section was updated to provide additional details on blinding during the 28-day randomized treatment study phase. Section 3.9 (Discontinuation of investigational product): This section was updated to emphasize that patients will discontinue when i-STAT potassium values are < 3.0 mmol/L at any time during the study or > 6.2 mmol/L during the 28-day randomized treatment study phase, and that discontinued patients must immediately receive appropriate medical treatment to manage their hypo- or hyperkalemia. In addition the discontinuation criteria for QTc prolongation were re-worded to align better with when QTc prolongation begins to represent a medical risk.
Section 4 (Table 1): The study plan and timing of procedures for the 48-hour open-label initial phase (Table 1) was updated as demographics will be collected and the IVRS/IWRS accessed on visit 1, and to reflect that AE collection will begin after the patient has signed informed consent. Throughout section 4, minor typographical errors and formatting was updated to improve the wording. Section 4.2 (Treatment period): This section was updated in line with the updates in Table1 and Table 2, and to clarify that sites may change the order of the procedures at a visit if agreed in advance with the sponsor study physician. Section 4.2.1 (48-hour open-label initial phase Day 1): This section was updated to clarify how to handle patients with i-STAT potassium <4.0 mmol/L at the 4 hour post Dose 1 blood draw. Section 4.2.3 (48-hour open-label initial phase Day 3): Vital signs were added to the study procedures in this section to align with Tables 1 and 2. Section 4.2.9 (28-day randomized treatment study phase Day 15): Vital signs were added to the study procedures in this section to align with Table 2. Section 4.2.13 (28-day randomized treatment study phase Day 29): Vital signs were added to the study procedures in this section to align with Table 2.

Section 4.3 (Follow-up period): Vital signs were added to the study procedures in this section to align with Table 2. Section 4: Figure 4 was added to provide the study flow chart based on the S-K level, which will be measured by i-STAT.
Section5.1 .1(Efficacy assessments-Potassium): This section was updated to better reflect the assessment for potassium throughout the study. Section 5.2.1 (Laboratory safety assessments): This section was updated to clarify that urine samples will be collected at the EOS visit. Section 5.2.2 (Physical examination): This section was updated to add targeted physical examination to the 48-hour open-label initial phase Day 3 procedures. Section 5.2.4.1 (Pulse Rate and blood pressure): More details were added to the description of how pulse rate and blood pressure will be assessed. Section 5.10 (Table 4): The footnote was updated to add an extra potassium assessment 90 minutes after taking the second dose of ZS for patients with i-STAT potassium ≥ 6.1 or < 4.0 mmol/L 4 hours after the first ZS Dose.
Section 6.3.1 (Time period for collection of adverse events): This section was updated to specify that Adverse Events (including SAEs) will be collected from the signing of the informed consent until the EOS visit.
Section 7.1 (Identity of investigational product): This section was updated to align with a change in drug packaging. Section 7.2 (Dose and treatment regimens): This section was updated to provide guidance on how to handle patients developing hypokalemia while receiving ZS. Section 7.7 (Concomitant and other treatments): This section was updated with more details on prohibited medications.
Section 8.2 (Sample size estimate): The sample size estimate text was revised to clarify that the study is powered for all test specified in the confirmatory testing sequence. Also, a typo was corrected to clarity that the standard deviation used in the sample size calculation was the “inter-subject standard deviation” and not the “intra-subject standard deviation. Section 8.3 (Definitions of analysis sets): The definition of the Full Analysis Set (FAS) and the Safety Analysis Set (SAF) were revised to align with the ICH E9- and CRGI Statistical Guidance. Section 8.4.3 (Safety Variables): This section was updated to include the physical examinations and ECGs as safety variables. Section 8.5 (Methods of statistical analyses): This section was revised to remove repetitive statements and to explicitly define the fixed hierarchical testing sequence of the study. Also, to include that sensitivity analyses will be performed to test the robustness of the primary and key secondary objectives.

Section 8.5.3 (Safety analysis): This section was updated to include the physical examinations and ECGs in the safety analysis. Section 8.5.4 (Analysis in subsets of patients): This section was revised to facilitate a benefit-risk assessment for the purpose of regulatory submission in both China and India.

Version 1.0, 20 April 2016
Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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.

CLINICAL STUDY PROTOCOL SYNOPSIS

A phase 3 multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS (sodium zirconium cyclosilicate), in patients with hyperkalemia-HARMONIZE Asia

International Co-ordinating Investigator

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Study site(s) and number of patients planned

This study will be conducted in approximately 35 centers in China. Before patients are randomized to the double-blind phase, they will receive open-label ZS for 24 or 48 hours during the initial phase. It is expected that approximately 490 patients will need to be enrolled, to have approximately 280 patients entered into the open-label initial phase resulting in 250 patients being randomized in the 28-day randomized treatment study phase. Enrolment will be stopped when 250 patients have been initiated with the 28-day randomized treatment study phase.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2021	Phase 3
Estimated date of last patient completed	Q1 2022	

Study design

This is a prospective, randomized, double-blind, placebo-controlled, phase 3 study to investigate the safety and efficacy of ZS in patients with hyperkalemia. This study consists of Pre-screening period which is optional, screening period (1 day), the open-label initial phase (24 or 48 hours), the 28-day randomized treatment study phase, and follow-up period (7±1 days after the last administration of study medication).

Optional Prescreening procedures will be performed, using i-STAT (A portable blood analyser) potassium values, to determine the consenting patients eligibility to enter the screening phase at Visit 1. If i-STAT potassium value is <5.1 mmol/L the patient will be declared a pre-screen failure. Screening procedures will be performed to determine patient eligibility during the screening period, and all baseline parameters should be measured/collected up to 1 day prior to administration of first dose of study drug on the open-label initial phase. In the open-label initial

phase, patients will receive open-label ZS at a dose of 10g per os (PO) three times a day (tid) for 24 or 48 hours, depending on potassium value. Once normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) is restored (whether after 24 or 48 hours, i.e., by the morning of Study Day 2 or Day 3), patients will then be randomized in the ratio of 2:2:1 into the double-blind 28-day randomized treatment study phase to receive ZS 5g once daily (qd), 10g qd or placebo qd for the following 28 days. Treatment will end on Day 29 visit, which will be followed by the end of study (EOS) visit taking place 7±1 days after the last administration of study medication.

For patients who do not enter the 28-day randomized treatment study phase, the last visit will be 7±1 days after the last treatment dose in the open-label initial phase.

Objectives

Primary Objective:	**Outcome Measure:**
To evaluate the efficacy of two different doses (5 and 10 g) of ZS orally administered once daily (qd) for 28 days in maintaining normokalemia (serum potassium [S-K] between 3.5-5.0 mmol/L, inclusive) in normokalemic patients following treatment in the open-label phase for hyperkalemic patients (two consecutive i-STAT potassium values ≥ 5.1 mmol/L, taken 60 minutes apart) at baseline.	Comparison between placebo and each ZS treatment group (high to low) with regard to the mean S-K level during the 28-day randomized treatment study phase Days 8-29.

Secondary Objectives:	**Outcome Measures:**
Open-label initial phase: • To evaluate the proportion of patients who achieve normokalemia after the completion of open-label initial phase treatment.	Open-label initial phase efficacy endpoints: • Proportion of patients who achieve normokalemia during the open-label initial phase at 24 hours and at the end of the open-label phase. • Exponential rate of change in S-K levels (blood) during the open-label initial phase. • Mean change (absolute and percent change) from baseline in S-K levels (blood) at all measured time intervals (See Table 1) post-dose during the open-label phase. • Time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/L, inclusive) during the open-label phase.
28-day randomized treatment study phase: • To evaluate the efficacy of ZS in patients with hyperkalemia for the following subgroups*: - chronic kidney disease (CKD) - diabetes mellitus (DM) - heart failure (HF) - those on renin-angiotensin-aldosterone system (RAAS) inhibitors. • To evaluate the effect of ZS on serum-Aldosterone (S-Aldo) and plasma-Renin (P-Renin) levels.	28-day randomized treatment study phase efficacy endpoints: • The proportion of patients who remain normokalemic (as defined by S-K between 3.5 5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during the 28-day randomized treatment study phase. • The number of days patients remain normokalemic during the 28-day randomized treatment study phase. • The mean change and mean percent change in S-K levels evaluated relative to both baselines. • The time to hyperkalemia (defined as S-K $\geq$ 5.1mmol/L). • The mean changes in S-Aldo and P-Renin levels.

* Primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase will be evaluated in patients with hyperkalemia for these subgroups. More details will be provided in the SAP.

Safety Objectives:	**Outcome Measures:**
• To evaluate the effect of ZS on other serum electrolytes in both the open-label initial phase and the 28-day randomized treatment study phase. • To evaluate the safety and tolerability profiles of ZS in both the open-label initial phase and the 28-day randomized treatment study phase.	• Serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]. • Adverse events (AEs), serious AEs (SAEs), vital signs (VS), physical examinations. • ECG • Clinical laboratory evaluations, including assessment of hypokalemia.

Target patient population

The target patient population includes male or female patients aged ≥ 18 to ≤ 90 years with hyperkalemia, defined as two consecutive i-STAT potassium values, measure 60-minutes apart, both ≥ 5.1mmol/L within 1 day of the first ZS dose.

Duration of treatment

The study may start with an optional Pre-screening visit. Patients with i-STAT potassium value is equal or more than 5.1 mmol/L will enter the screening. The study will follow with a screening period, and all baseline parameters should be measured/collected up to 1 day prior to administration of first dose of study drug on the open-label initial phase Day 1.

During the open-label initial phase, patients will receive ZS per os (PO) at a dose of 10g three times a day (tid) for 24 or 48 hours, depending on potassium value. Once normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) is restored (whether after 24 or 48 hours, i.e., by the morning of Study Day 2 or Day 3), patients will then be randomized in a ratio of 2:2:1 to the double-blind 28-day randomized treatment study phase to receive ZS 5g, 10g or placebo, PO qd for the following 28 days. Patients in the double-blind treatment phase will be required to complete the Day 29 visit and the EOS visit which is 7±1 days after the last administration of study medication. For patients who do not enter the 28-day randomized treatment study phase the last visit will be 7±1 day after the last treatment dose in the open-label initial phase. The total expected study duration for each individual patient is approximately 5-6 weeks.

Investigational product, dosage and mode of administration

Open-label initial phase:

- ZS 10g will be administered orally three times a day (tid) for 24 or 48 hours as an oral suspension.

28-day randomized treatment study phase:

- ZS 5g will be administered orally once daily (qd) for 28 days as an oral suspension.
- ZS 10g will be administered orally once daily (qd) for 28 days as an oral suspension.
- Matching Placebo for ZS will be administered orally once daily (qd) for 28 days as an oral suspension.

Please note: If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive, during the open-label initial treatment phase, the patient will be directed to not take any more ZS for the remainder of that day and return the next day to assess potassium, if the potassium is then between 3.5 and 5.0 mmol/L, the patient will be randomized.

If a patient develops i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval), during the 28-day randomized treatment study phase, dosing will be reduced from qd to once every other day (qod) for the remainder of the study.

Patients with confirmed i-STAT potassium <3.0 mmol/L in both phases should discontinue from therapy.

Patients with confirmed i-STAT potassium >6.2 mmol/L during the 28-day randomized treatment study phase should discontinue from therapy.

Statistical methods

Separate efficacy and safety analyses will be performed for the open-label initial phase and the 28-day randomized treatment study phase. All patient analysis sets will be confirmed and documented in a Statistical Analysis Plan (SAP) prior to database lock. The study will have prospectively defined patient analysis sets for the open-label initial phase and 28-day randomized treatment study phase.

For the open-label initial phase, the full analysis set will include all patients registered in the open-label initial phase. The safety analysis set, for the open-label initial phase, will include all patients with at least one dose of IP during this treatment phase, and will be analyzed on an as-treated basis.

For the subsequent 28-day randomized treatment study phase, the full analysis set will include all randomized patients. The safety analysis set, for the 28-day randomized treatment study phase, will include all patients with at least one dose of the 28-day randomized treatment study phase IP among those randomized, and will be analyzed on an as-treated basis.

Unless otherwise specified, all efficacy analyses will be carried out on the full analysis sets, which is based on the Intension-to-Treat (ITT) principle; and all safety analyses will be based on the safety analysis sets.

The null hypothesis for the study is that there is no treatment difference (in mean S-K levels Days 8-29) between each ZS dose (high to low) versus placebo control. The alternative hypothesis is that ZS is more effective than the placebo control in maintaining mean 28-day randomized treatment study phase Day 8-29 serum potassium levels (3.5-5.0 mmol/L, inclusive) among hyperkalemic patients in whom normokalemia is established during the open-label initial phase.

All efficacy analyses will be based on the S-K values obtained from the Central Laboratory. If Central Laboratory data are missing, they will be replaced by i-STAT values adjusted with the mean paired difference between i-STAT and S-K values collected at the same visit. More details on how to handle dropouts and missing data will be provided in the SAP.

The primary endpoint in the study will be the model-based least squares means (LSMEANS) of all available S-K values during the 28-day randomized treatment study phase Days 8-29. A log transformation will be applied to the S-K levels, since historical data shows that S-K measurements follows a log-normal distribution, and also to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (high to low) versus placebo control for the 28-day randomized treatment study phase to estimate the least squares means Day 8-29 values. The model will include all S-K data collected at the scheduled visits between Day 8-29 as response variables, with baseline covariates for the open-label initial phase eGFR, the open-label initial phase S-K values, the 28-day randomized treatment study phase S-K values as well as age (<55, 55-64, >64 years), country and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, and diabetes mellitus as fixed effects terms and patients are random effect term. In addition, the primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase will be evaluated for the subgroups (i.e., CKD DM, HF and those on RAAS inhibitors). More details will be described in the SAP.

Secondary efficacy endpoints will include:

- The proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during the 28-day randomized treatment study phase.
- The number of days patients remain normokalemic during the 28-day randomized treatment study phase.
- The mean change and mean percent change in S-K levels evaluated relative to both baselines.
- The time to hyperkalemia (defined as S-K $\geq$ 5.1 mmol/L).
- The mean change in S-Aldo and P-Renin levels.

Safety endpoints will include adverse events (AEs), serious AEs (SAEs), vital signs, clinical laboratory evaluations, physical examinations, ECGs, and other serum electrolytes (specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO_4], serum bicarbonate [S-HCO_3], and blood urea nitrogen [BUN]).

The confirmed i-STAT potassium value on Study Day 2 or Day 3 of the open-label initial phase will be used to established the patient's eligibility into the 28-day randomized treatment study phase, however central laboratory S-K values will be used for all analyses.

Sensitivity analyses will be conducted to assess the robustness of the results of the primary analysis and the secondary analysis of the proportion of normokalemic patients at the end of the 28-day randomized treatment study phase and during the 28-day randomized treatment study phase.

There is no planned interim analysis in this study.

Assuming an inter-subject standard deviation of 0.50, approximately 250 patients, (100 patients per active dose treatment arm and 50 patients for placebo control arm), will provide >90% power to detect a mean difference of 0.30 in mean 28-day randomized treatment phase Day 8-29, comparing each active dose (high to low) vs. placebo control using a two-sided t-test at a significance level of 5%. Assuming 90% of patients will be normokalemic after treatment in the open label initial phase (see Section 7.2), approximately 280 patients will be needed to enter the open-label initial phase.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACE	Angiotensin-converting-enzyme
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARBs	Angiotensin-receptor blockers
AST	Aspartate aminotransferase
AZ	AstraZeneca
AZRand	AZ global Randomization System
BP	Blood pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
FAS-OLP	Full Analysis Set for the Open-Label Initial Phase
FAS-RTP	Full Analysis Set for the 28-day Randomized Treatment Study Phase
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate

Abbreviation or special term	**Explanation**
GGT	Gamma-glutamyl transferase
ICF	Informed Consent Form
ICH	International Conference on Harmonization
International Co-ordinating investigator	The Investigator co-ordinating the investigators and/or activities internationally
ITT	Intent-to-Treat
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HF	Heart Failure
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PGx	Pharmacogenetic research
PI	Principal Investigator
PO	Per Os
PP	Per Protocol
P-Renin	Plasma-Renin
qd	once daily
qod	every other day
RAAS	Renin-angiotensin-aldosterone system
RBC	Red Blood Cell
S-Aldo	Serum-Aldosterone
SAE	Serious adverse event
SAF	Safety Analysis Set
SAF-OLP	Safety Analysis Set for the Open-Label Initial Phase
SAF-RTP	Safety Analysis Set for the 28-day Randomized Treatment Study Phase
SAP	Statistical Analysis Plan
SARs	Suspected Adverse Reactions
S-Ca	Serum calcium
S-HCO3	Serum bicarbonate

Abbreviation or special term	Explanation
S-K	Serum potassium
S-Mg	Serum magnesium
S-Na	Serum sodium
S-PO4	Serum phosphate
SPS	Sodium Polystyrene Sulfonate
SST	Serum Separator Tube
tid	three times a day
VS	Vital Sign
WBC	White Blood Cell
WBDC	Web Based Data Capture
WHODrug	World health Organization Drug Dictionary
ZS	Sodium Zirconium Cyclosilicate (SZC)

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Potassium is a ubiquitous ion, involved in numerous processes in the human body. It is the most abundant intracellular cation and is critically important for numerous physiological processes, including maintenance of cellular membrane potential, homeostasis of cell volume, and transmission of action potentials. The main dietary sources are vegetables (tomatoes and potatoes), fruit (oranges, bananas) and meat. The normal potassium values in serum (S-K) are between 3.5 and 5.0 mmol/L, with the kidney being the main regulator of potassium values. The renal elimination of potassium is passive (through the glomeruli) with active reabsorption in the proximal tubule and the ascending limb of the loop of Henle. There is active excretion of potassium in the distal tubules and the collecting duct, both of which processes are controlled by aldosterone.

Hyperkalemia develops when there is excessive production (oral intake, tissue breakdown) or insufficient elimination of potassium. Insufficient elimination, which is the most common cause of hyperkalemia, can be hormonal (as in aldosterone deficiency), pharmacologic (treatment with angiotensin-converting-enzyme [ACE] inhibitors or angiotensin-receptor blockers [ARBs]) or, most commonly, due to reduced kidney function. Increased extracellular potassium values result in depolarization of the membrane potential of cells. This depolarization opens some voltage-gated sodium channels, but not enough to generate an action potential. After a short period of time, the open sodium channels inactivate and become refractory, increasing the threshold to generate an action potential. This leads to impairment of the neuromuscular, cardiac, and gastrointestinal organ systems, and is responsible for the symptoms seen with hyperkalemia. Of

greatest concern is the effect on the cardiac system, where impairment of cardiac conduction can lead to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. Because of the potential for fatal cardiac arrhythmias, hyperkalemia represents an acute metabolic emergency that must be immediately corrected.

The most common cause of hyperkalemia is renal insufficiency, and there is a close correlation between the degree of kidney failure and S-K values. In addition, a number of different commonly used drugs can cause hyperkalemia, such as ACE inhibitors, ARBs, potassium-sparing diuretics (e.g., amiloride, spironolactone), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen, celecoxib), heparin, and certain cytotoxic and antibiotic drugs (e.g., cyclosporin and trimethoprim). Finally, beta-receptor blocking agents, digoxin or succinylcholine are other well-known causes of hyperkalemia. In addition, advanced degrees of heart failure (HF), massive injuries, burns, or intravascular hemolysis cause hyperkalemia as can metabolic acidosis, most often as part of diabetic ketoacidosis.

Symptoms of hyperkalemia are non-specific and include malaise and muscle weakness or signs of cardiac arrhythmias, such as palpitations, bradycardia, or tachycardia. Often, however, the hyperkalemia is detected during routine screening blood tests for a medical disorder, or after complications have developed, such as cardiac arrhythmias or sudden death.

Diagnosis is established by S-K or plasma potassium measurements. Serum potassium values are most commonly used for diagnosis and to evaluate treatment response.

Treatment of hyperkalemia depends on the S-K values. In mild to moderate hyperkalemia acute treatment with a potassium-binding resin, combined with dietary advice (low potassium diet) and possibly modification of drug treatment (if treated with drugs causing hyperkalemia) will be standard of care. In severe hyperkalemia, or if arrhythmias are present, emergency lowering of potassium and close monitoring in a hospital setting are mandated.

- Sodium polystyrene sulfonate (sodium polystyrene sulfonate [SPS]; e.g., Kayexalate) is a resin that binds potassium in the intestine and increases fecal excretion, thereby reducing S-K values. However, as SPS has been shown to cause intestinal obstruction and potential rupture, diarrhea needs to be simultaneously induced, significantly reducing the palatability of the treatment. Even without the induction of diarrhea, a substantial proportion of patients complain of gastrointestinal symptoms, such as constipation, abdominal pain, cramping, distension, nausea, and vomiting. In addition, SPS is non-specific and also binds calcium and magnesium, thereby increasing the risk of inducing hypocalcemia and/or hypomagnesemia.

- Intravenous insulin (administered with or without glucose to prevent hypoglycemia) to shift potassium into the cells and away from the blood.

- Intravenous calcium gluconate or chloride decreases myocardial excitability and stabilizes the myocardium, reducing the risk for cardiac arrhythmias, but does not affect S-K.

- Severe cases not responding to other medical therapy may require dialysis.

Thus, the only pharmacologic therapy that increases elimination of potassium from the body is SPS. However, due to the need to induce diarrhea, SPS cannot be administered on a chronic basis. Even in the acute setting, the need to induce diarrhea, combined with inconsistent efficacy and a foul smell and taste, reduces the usefulness of SPS. Hence, there is a significant medical need for new and better treatment modalities for the acute as well as chronic treatment of hyperkalemia.

ZS-9 is a microporous zirconium silicate with a specific crystal geometry that confers a high, selective exchange capacity for potassium and ammonium ions. Sodium zirconium cyclosilicate (ZS) is a partially protonated form of ZS-9 that is being developed for the treatment of hyperkalemia.

ZS has been shown to bind potassium in the intestine of animals in exchange for hydrogen and sodium. The potassium-binding capacity of ZS has been shown *in vitro* to be approximately 10 times that of SPS in the presence of calcium and magnesium cations, which would represent a significant therapeutic advantage over SPS. *In vivo* studies in dogs and rats demonstrated significant dose-related reductions in the fractional excretion of urinary potassium up to 95% without any change in serum magnesium or calcium levels. Toxicology studies have shown ZS to be well tolerated at doses up to ~2.3-fold higher than the maximum three times a day ZS dose planned for registration or ~14-fold higher than the recommended starting once daily dose of 5 g per day. In addition, animal studies have demonstrated that ZS is not systemically absorbed, but exerts its effects locally in the gastrointestinal tract, significantly reducing the risk of any systemic toxicity.

As of September 2019, the clinical efficacy and safety of ZS in the treatment of hyperkalaemia has been assessed in 9 Phase 2/Phase 3 studies: 6 randomised, double blind, placebo controlled studies and 3 open label dose titration studies. In these studies, 2343 subjects with hyperkalaemia received at least 1 dose of ZS.

Clinical studies in subjects with hyperkalaemia consistently demonstrated that initial treatment with ZS 10 g tid for 24 h up to 72 h resulted in clinically meaningful S-K reduction with a majority of subjects achieving normokalaemia within 24 to 48 hours. Moreover, subjects with higher baseline S K levels had greater reductions in S K levels. Onset of efficacy was rapid with S-K reduction observed as early as 1 hour after dose intake.

After correction of hyperkalaemia, continued maintenance treatment for 28 days with ZS 5 g, 10 g, or 15 g qd resulted in continued effective control of S K within the normokalemic range. The proportion of subjects who remained normokalemic at the end of treatment with ZS 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 ZS utilising 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 normokalaemia in the majority of subjects.

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

1.2 Rationale for study design, doses and control groups

This phase 3 study was intended to be included in applications for marketing authorization in the countries where the study is performed. ZS was approved in China for hyperkalemia based on overseas data at the end of 2019, now this is a post-approval commitment study for China.

A double-blind, placebo-controlled, randomized study represents the optimal design for obtaining unbiased estimates of treatment group differences for a new drug under development. Recognizing that all patients will receive active treatment during the open-label initial phase, combined with the fact that all patients will be monitored in the clinic for at least 4 hours after the initial dose of ZS, the level of hyperkalemia that could be included is not limited.

The randomized portion of the study (the 28-day randomized treatment study phase) is designed to assess whether extended administration of ZS maintains control of S-K values and to demonstrate that hyperkalemia recurs once ZS is withdrawn. Such design represents state-of-the-art in demonstrating the need for ongoing longer-term treatment of a new drug under development. A 28-day randomized treatment study phase is selected as a compromise between ensuring a sufficiently long treatment period to demonstrate that ZS can maintain normokalemia over extended time, while not exposing patients with a potentially life-threatening condition to extended treatment with placebo. Eligibility for the open-label initial phase, eligibility for the 28-day randomized treatment study phase, and potassium-related stopping criteria are based on i-STAT measurements as these decisions need to be made in 'real-time' due to the risk of potentially life-threatening cardiac arrhythmias associated with severe hyperkalemia or hypokalemia. However, all endpoint analyses will be based on standardized S-K measurements analyzed at a central laboratory. For treatment decisions (i.e., S-K values on i-STAT < 3.5 mmol/L), a second i-STAT sample will be taken 10 minutes after the initial abnormal sample to ensure that treatment is only changed once hypokalemia is confirmed. For a treatment decision to be made, both samples, taken 10 minutes apart, need to be below 3.5 mmol/L.

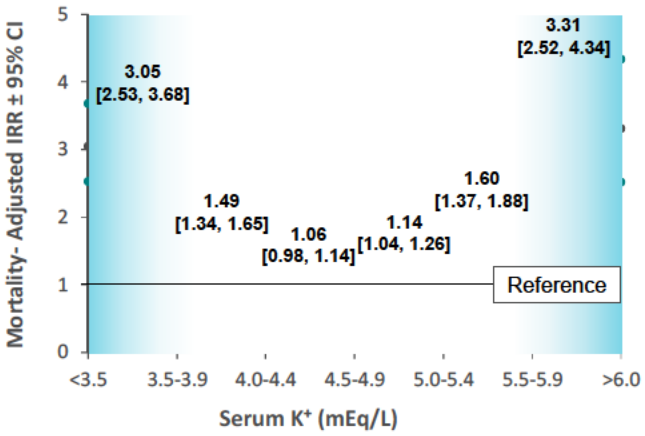
The design of this study is similar to the global ZS-004 study. In study ZS-004 (Kosiborod M et al 2014), ZS was highly effective in reducing S-K in patients with hyperkalemia, demonstrating statistically significant improvement from baseline in S-K with ZS 10 g TID over the first 48 hours of dosing. Patients who achieved normokalemia after receiving ZS 10 g TID in the Acute Phase were randomized to 28 days of placebo, ZS 5 g qd, ZS 10 g qd, or ZS 15 g qd dosing during the Maintenance Phase. ZS was effective in maintaining normokalemia (S-K between 3.5 mmol/L and 5.0 mmol/L, inclusive), meeting the predefined primary efficacy endpoint of mean S-K value during Maintenance Phase Study Days 8 to 29 at all 3 doses of ZS. Treatment with ZS was well tolerated in the patients recruited in ZS-004. The doses studied in this study were selected considering both efficacy and tolerability of the doses studies in ZS-004. Specific exclusion criteria ensure that appropriate patients, who are not at excess risk from treatment, will be enrolled. The multicenter design enhance the external validity, reproducibility, and generalizability of the results observed.

The patient selection criteria allows for the assessment of both efficacy and safety of ZS in a relevant population of patients with hyperkalemia. Since hyperkalemia affects both men and women, the inclusion criteria allows equal access to the protocol for both sexes. Exclusion criteria are developed based on consideration of safety concerns and to prevent enrollment of patients who are unsuitable for the study. In order to ensure the study population reflect 'real life', the exclusion criteria are not extensive, as the Sponsor want to ensure that the patient population enrolled is representative of the patient population receiving the drug post-approval. Hence, a large number of concomitant diseases and concomitant treatments are allowed, recognizing that many patients with hyperkalemia would also suffer from a range of concomitant diseases. This approach was further justified by the favorable safety and tolerability profile observed in Study ZS-003 and Study ZS-004, combined with the fact that ZS is not systemically absorbed.

1.3 Benefit/risk and ethical assessment

Hyperkalemia is common in patients with chronic kidney disease, or heart failure, particularly when treated with renin angiotensin aldosterone system inhibitors (RAASi). Mortality risk with hyperkalemia parallels the magnitude of potassium elevation.

Figure 1 **Multivariable-adjusted mortality by serum potassium level in a cohort of 55,266 patients with eGFR <60 ml/min per 1.73 m2 during median follow up 2.76 years (Lou J et al 2016)**



For acute treatment, intravenous glucose/insulin and inhaled beta-adrenergic agonists drive potassium into cells. Potassium can be removed from the body by dialysis or with non-absorbed polymers which non-selectively bind potassium and are excreted. Polymers do not lower potassium rapidly and cause significant gastrointestinal (GI) side effects (colonic necrosis, bowel obstruction, GI bleeding, ischemic colitis, perforation), bind to many oral medications and to other cations, lowering magnesium and calcium levels. Thus, an unmet need remains for safe, rapid, and an effective treatment for hyperkalemia.

Sodium zirconium cyclosilicate (ZS) is a non-absorbed, inorganic crystal that selectively exchanges hydrogen and sodium cations for potassium in a dynamic process throughout the upper and lower gastrointestinal tract. Bound potassium ions are excreted from the body. ZS is

a white, insoluble, powder provided in 5g and 10g sachets to be suspended in water for oral administration.

1.3.1 Clinical benefits

In randomized, double-blind, placebo-controlled trials, ZS rapidly corrected potassium levels and maintained normokalemia in patients with hyperkalemia including those with chronic kidney disease, heart failure, diabetes mellitus and RAASi use. ZS was effective regardless of the underlying cause of hyperkalemia, age, sex, race or baseline potassium level.

ZS acts rapidly, statistically significantly reducing potassium within one hour (study ZS-003). With ZS10g TID, 77% of patients achieved normokalemia within 24 hours and 86% within 48 hours. Median time to normokalemia was 2.2 hours (ZS-004).

ZS is self-equilibrating. Potassium fell 0.8, 1.2 and 1.5 mmol/L at 48 hours among patients with baseline potassium <5.5, 5.5-5.9 and ≥6.0 mmol/L, respectively (ZS-004). Self-equilibration reduces the risk of hypokalemia and reflects the mechanism of action; as potassium levels normalize, less potassium is excreted into the GI tract and fewer cations are exchanged.

ZS maintains normokalemia. Patients who achieved normokalemia with TID dosing were randomized to maintenance therapy with once daily ZS or placebo for 12 days (ZS-003) or 28 days (ZS-004). ZS-003 met predefined efficacy endpoints at the 5 and 10g doses when compared with placebo. In ZS-004, ZS 5, 10 or 15g increased the number of normokalemic days ($p \leq 0.0001$ for each dose vs placebo) and maintained potassium at lower levels than placebo ($p \leq 0.0001$ for all doses). ZS maintained normokalemia for up to 12 months in the open label extension; when ZS was stopped, potassium rose to near baseline levels (ZS-004E).

Co-administration of ZS with clopidogrel, dabigatran, glipizide, losartan, furosemide, atorvastatin, amlodipine, warfarin, and levothyroxine identified no clinically meaningful drug-drug interaction (ZS-009).

1.3.2 Clinical risks

The safety of ZS was evaluated in clinical trials for the reduction of hyperkalemia involving over 1,500 patients.

The most commonly reported adverse reaction was edema related events which were reported by 5.7% ZS patients; 1.7, 2.7, 5.2, and 14.3% of patients randomized to placebo, ZS 5 g, 10 g, or 15 g once daily up to one month, respectively. Fifty-three percent were managed with initiating a diuretic or adjusting a diuretic dose; the remainder did not require treatment.

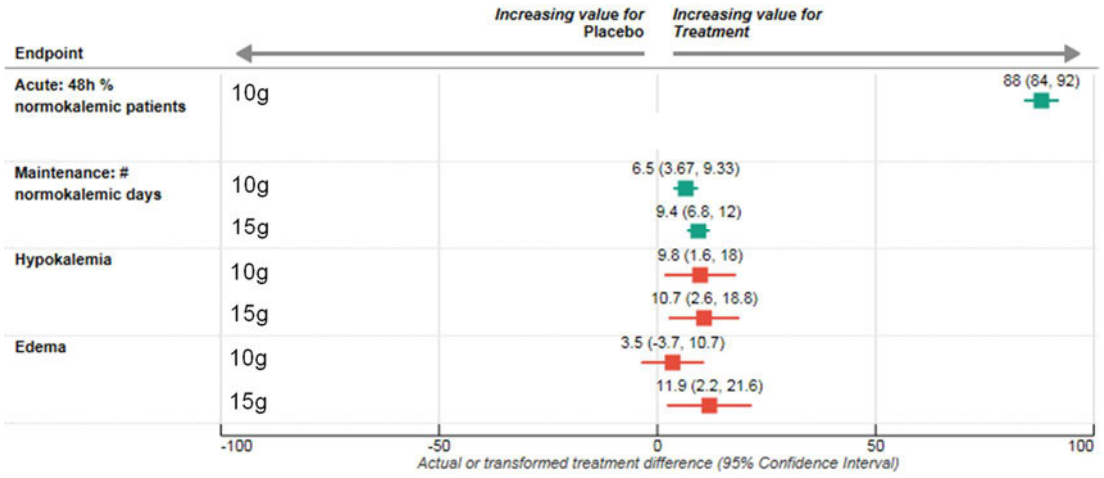
In clinical trials, 4.1% of ZS patients developed hypokalemia with a serum potassium value less than 3.5 mmol/L, which was resolved with dose adjustment or discontinuation of ZS.

1.3.3 Clinical benefit-risk balance

For correction of hyperkalemia, ZS 10g TID is recommended for up to 3 days until normokalemia is achieved. Thereafter, maintenance therapy is initiated with 5g qd and dose adjusted from 10g daily to 5g every other day to maintain normokalemia.

Benefits and risks for ZS are summarized below:

Figure 2 Forest plot of benefits (green) and risks (red) for ZS 10g and 15g



Hyperkalemia increases the risk of arrhythmic death; potassium lowering reduces this risk even if normokalemia is not achieved. Benefits of ZS over placebo in patients with hyperkalemia include rapidly reducing serum potassium to achieve normokalemia and maintenance of normokalemia. Advantages over currently available therapies include rapidity of potassium lowering, no clinically meaningful drug-drug interactions, no increase in gastrointestinal adverse events or hypomagnesemia.

The risks identified with ZS treatment include hypokalemia and edema-related events. In this study, the risk for hypokalaemia is mitigated by periodic monitoring of potassium and adjustment of the dose of IP as necessary. Edema can be managed in line with standard clinical practice. No additional safety risks have so far been identified.

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

1.3.4 Conclusions

Based on available data, the benefit-risk assessment for sodium zirconium cyclosilicate is favourable for correction of hyperkalemia (10g TID for up to 3 days) and for maintenance treatment of patients with hyperkalemia across the dose range 15g daily to 5g every other day.

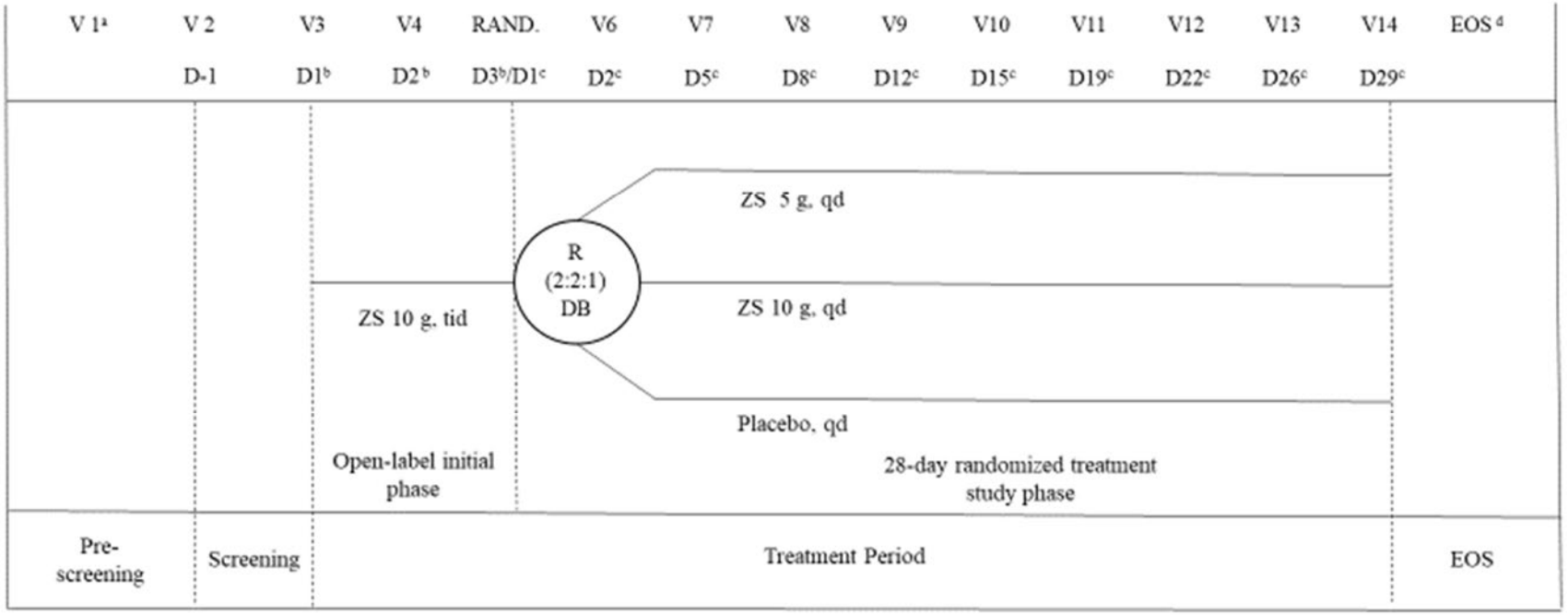
1.4 Study Design

This is a prospective, randomized, double-blind, placebo-controlled, phase 3 study to investigate the safety and efficacy of ZS in patients with hyperkalemia.

This study consists of the optional Pre-screening period, the screening period (1 day), the open-label initial phase (24 or 48 hours), the 28-day randomized treatment study phase and EOS visit which is 7±1 days after the last administration of study medication. For patients who failed in pre-screening and screening, the standard of care at the discretion and the direction will be given by his/her own physician. For patients who do not enter the 28-day randomized treatment study phase the last visit will be 7±1 day after the last treatment dose in the open-label initial phase.

The study comprises 14-15 visits: optional Pre-screening visit (Visit 1), enrolment visit (Visit 2), entering visit to the open-label initial phase (Visit 3), treatment visit in the open-label initial phase (Visit 4, only for those not achieving normokalemia after 24 hours treatment), randomization visit to the 28-day randomized treatment study phase, treatment visit in the 28-day randomized treatment study phase (Visit 6-13), safety visit in the 28-day randomized treatment study phase (Visit 14), and end of study (EOS) visit. For details on timing of visits, see Figure 3 below:

Figure 3 Study flow chart



R=Randomization; DB=Double-blind; EOS=End of study; V=Visit, D=Day, tid=three times a day; qd=once daily

[a] Pre-screening visit is optional. Patients who participate in the Pre-screening visit and meet all Pre-screening inclusion/exclusion criteria will be entered into the screening part of the study within 7 days.

[b] Study Day for open-label initial phase, patients achieving normokalemia in the morning of Day 2 of the open-label initial phase will enter Study Day 1 of the 28-day randomized treatment phase directly.

[c] Study Day for 28-day randomized treatment study phase. Day 3 of the open-label initial phase is the same day as Day 1 for 28-day randomized treatment study phase. For patients achieving normokalemia by the morning of Day 2 of the initial phase, that day would be the same day as Day 1 for 28-day randomized treatment study phase.

[d] EOS occurs 7±1 day after the last administration of study medication (same applies if patients leave the study during open-label initial phase)

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To evaluate the efficacy of two different doses (5 and 10 g) of ZS orally administered once daily (qd) for 28 days in maintaining normokalemia (serum potassium [S-K] between 3.5-5.0 mmol/L, inclusive) in normokalemic patients, following treatment in the open-label initial phase, for hyperkalemic patients (two consecutive i-STAT potassium values ≥ 5.1 mmol/L, taken 60 minutes apart) at baseline.	Comparison between placebo and each ZS treatment group (high to low) with regard to the mean S-K level during the 28-day randomized treatment study phase Days 8-29.

2.2 Secondary objectives

Secondary Objectives:	**Outcome Measures:**
Open-label initial phase: • To evaluate the proportion of patients who achieve normokalemia after the completion of open-label initial phase treatment. 28-day randomized treatment study phase: • To evaluate the efficacy of ZS in patients with hyperkalemia for the following subgroups as applicable*: - chronic kidney disease (CKD) - diabetes mellitus (DM) - heart failure (HF) - those on renin-angiotensin-aldosterone system (RAAS) inhibitors • To evaluate the effect of ZS on serum-Aldosterone (S-Aldo) and Plasma-Renin (P-Renin) levels.	Open-label initial phase efficacy endpoints: • Proportion of patients who achieve normokalemia during the open-label initial phase at 24 hours and at the end of the open-label phase • Exponential rate of change in S-K levels (blood) during the open-label initial phase • Mean change (absolute and percent change) from baseline in S-K levels (blood) at all measured time intervals (See Table 1) post-dose during the open-label phase • Time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/L, inclusive) during the open-label phase 28-day randomized treatment study phase efficacy endpoints: • The proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during the 28-day randomized treatment study phase • The number of days patients remain normokalemic during the 28-day randomized treatment study phase • The mean change and mean percent change in S-K levels evaluated relative to both baselines • The time to hyperkalemia (defined as S-K ≥ 5.1mmol/L) • The mean changes in S-Aldo and P-Renin levels

* Primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase will be evaluated in patients with hyperkalemia for the subgroups. More details will be described in the SAP.

2.3 Safety objectives

Safety Objectives:	**Outcome Measures:**
• To evaluate the effect of ZS on other serum electrolytes in both the open-label initial phase and the 28-day randomized treatment study phase. • To evaluate the safety and tolerability profiles of ZS in both the open-label initial phase and the 28-day randomized treatment study phase.	• Serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN] • Adverse events (AEs), serious AEs (SAEs), vital signs (VS), physical examinations • ECG • Clinical laboratory evaluations, including assessment of hypokalemia

2.4 Exploratory objectives (Not applicable)

3. PATIENT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

Optional Pre-screening part of the study

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent (pre-screening consent) prior to any study specific procedures

2. Female and male patients aged ≥18 and ≤ 90 years

Main part of the study

Above inclusion criteria 2 is also applied to the Main part of the study. In addition, for inclusion in the study patients should fulfil the following criteria:

3. Provision of informed consent prior to any study specific procedures

4. Two consecutive i-STAT potassium values, measured 60-minutes (± 10 minutes) apart, both ≥ 5.1 mmol/L and measured within 1 day of the first ZS dose on open-label initial phase Day 1

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

6. Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of ZS/matching placebo to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.

Note: Whenever possible, all blood draws collected prior to meals should be collected prior to insulin/insulin analog treatment.

3.2 Exclusion criteria

Optional Pre-screening part of the study

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Participation in another clinical study with an investigational product during the last 3 months

3. Presence of any condition which, in the opinion of the investigator, places the patient at undue risk or potentially jeopardizes the quality of the data to be generated

Main part of the study

Above exclusion criteria are also applied to the Main part of the study. In addition, patients should not enter the study if any of the following exclusion criteria are fulfilled:

4. Pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen due to excessive fist clenching to make veins prominent, difficult or traumatic venepuncture, or history of severe leukocytosis or thrombocytosis

5. Patients treated with lactulose, xifaxan (rifaximin) or other non-absorbed antibiotics for hyperammonemia within 7 days prior to the first dose of study drug

6. Patients treated with resins (such as sevelamer acetate or sodium polystyrene sulfonate [SPS; e.g., Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within 7 days prior to the first dose of study drug

7. Patients with a life expectancy of less than 3 months

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

9. Female patients who are pregnant, lactating, or planning to become pregnant

10. Patients with diabetic ketoacidosis

11. Known hypersensitivity or previous anaphylaxis to ZS or to components thereof

12. Patients with cardiac arrhythmias that require immediate 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. Subjects with atrial fibrillation controlled by medication are permitted

16. QTc(f) > 550 msec

17. Patients on dialysis

18. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of ZS

19. Patients who need hospitalization after taking blood samples on day 1 of the open-label initial phase

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomization

Patients enrolling in the study will provide consent in a two-stage process. Investigator(s) should keep a record provided by the sponsor, the patient screening log, of any patients who are considered for entering the pre-screening.

Optional Pre-screening part of the study

The Investigator(s) will:

1. Obtain signed Pre-screening informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed.

2. Consent to Pre-screening will be closed once sufficient patients have been enrolled to reach the required number of randomised patients.

Main part of the study

Patients who are eligible for participation in the study, will subsequently be offered the option of consenting to the main study and will need to sign the main study consent, in addition to the first consent. They will then undergo all other screening assessments for the screening part of study.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form (ICF).

2. Assign potential patients a unique enrolment number via IVRS/IWRS, beginning with 'E#'.

3. Patients will remain associated with the same patient number throughout the entire study, and patients should NOT receive any new E-code if re-screened. If a patient signs the ICF but does not meet the inclusion/exclusion criteria the patient will be marked as a screen failure on the Screening and Enrolment Log provided by the Sponsor and will be entered in Web Based Data Capture (WBDC) as a screen failure. Patients can be re-screened once. A new ICF does not need to be signed before re-screening if the original ICF was signed within 30 days and the ICF has not been revised.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The randomization codes will be computer generated using the AZ global randomization system (AZRand) and loaded into the IVRS/IWRS database. Randomization codes will be generated in blocks to ensure approximate balance (2:2:1) between the three treatment arms (ZS 5g or ZS 10g or placebo once daily). Randomization will be stratified by country.

3.6 Methods for ensuring blinding

The 28-day randomized treatment study phase will have a double blind design. Patients will take by mouth the entire contents of a single sachet qd, containing either ZS 5g, ZS 10g or placebo. The exterior of the sachets are identical. Individual sachets are enclosed in a carton with a tamper evident seal intended to be broken exclusively by patients just before taking the study drug.

No member of the study team at AZ, or representative, personnel at study centers or any clinical research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study, with the exception of the AZ personnel generating the randomization scheme as well as AZ Supply Chain, the Patient Safety data entry site and the CRO companies providing the IVRS/IWRS and carrying out the packaging and labeling of study medication. This documentation will be kept in a secure location until the end of the study.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient in the 28-day randomized treatment study phase, will be available to the Investigator(s) from the IVRS/IWRS in case of unblinding situation. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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

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

3.8 Restrictions

Patients on RAAS inhibitors and/or diuretics are not allowed to titrate or discontinue or switch RAAS inhibitors and/or diuretic therapy during the study. For concomitant medications which are restricted during the study, please see Section 7.7.

3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event

- Severe non-compliance with the study protocol
- Risk to patient as judged by investigator
- Pregnancy
- Require treatment with medications prohibited or contraindicated for use due to safety concerns with ZS
- Start dialysis while in the study
- Patient unblinded due to emergency
- Patients who change or switch RAAS inhibitor and/or diuretic dose during the study
- Patient develops severe hypokalemia (i-STAT potassium values <3.0 mmol/L) at any time during the study or has i-STAT level > 6.2 mmol/L during the 28-day randomized treatment study phase (confirmed by taking a second potassium measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug discontinuation rule). Patients discontinuing due to this criterion must immediately receive appropriate medical treatment to manage their hypo- or hyperkalemia.
- Patient has a clinically significant cardiac arrhythmia (see below) at any time in the 28-day randomized treatment study phase, the patient should immediately receive appropriate medical treatment and be discontinued from study drug. Any of the following cardiac events will result in immediate discontinuation from the study drug (independent of whether it is in the open-label initial phase or the 28-day randomized treatment study phase):
  - Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, new paroxysmal supraventricular tachycardia [other than sinus tachycardia], new 2nd or 3rd degree AV block or significant bradycardia [HR < 40 bpm])
  - Acute heart failure
  - Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block), widening of the QRS complex (>140 msec in the absence of pre-existing bundle branch block) or new onset peaked T-wave
  - An absolute QTc >550msec, or an increase in QTc interval > 60msec from baseline to more than 500msec. All patients meeting the QTc>500ms criterion should immediately have potassium assessed by i-STAT and central lab, if not already done within 1 hour of the collection of the ECG. The QTc(f) algorithm (QT interval corrected by the Fridericia method) is recommended.

Patients who discontinue from study medication during the 28-day randomized treatment study phase but agree to remain in the study should continue to follow protocol-specified procedures and assessments except for dispensing of study medication for the study.

Any patient who is discontinued from the study treatment during open-label initiation phase will return to the clinic 7 (± 1) days after the last IP administration for an EOS visit. Note: Discontinuation of investigational product does not necessarily imply discontinuation of follow-up or termination of all study participation.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up; and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

The term withdrawal from the study refers to discontinuation from both study medication and study assessments.

Specific reasons for withdrawal from study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment (see Section 3.10.2)
- Severe non-compliance to protocol as judged by the Investigator and/or Sponsor
- Patient lost to follow-up
- Death

The date and reason for patient withdrawal must be recorded on the appropriate electronic Case Report Form (eCRF). Every attempt should be made to contact any patient considered lost to follow-up.

It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be entered into the study, i.e., patients that are withdrawn prior to receiving open label treatment. These patients should have the reason for study withdrawal recorded as ‘Eligibility criteria not fulfilled’ (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that are assessed as causally related to study drug and are not considered to be consistent with continuation of the study.

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan detailing the procedures: optional Pre-screening, screening and open-label initial phase

Study Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[8]**	**Rand. Visit**	**EOS[10]**
Initial Phase Day	**Pre-screen [3]**	**Screen**	**Day 1[14]**	**Day 2[14]**	**Day 2 or 3[14]**	**Day 9 (±1d)**
Accepted visit window during prolonged public holidays[18]						**Day 4-16**
Written informed consent	X	X				
Eligibility criteria	X		X[11]		X	
Demographics	X	X				
Medical History			X[11]			
Physical exam including weight			X[11, 15]		X[15]	X[15]
Access IVRS/IWRS		X	X		X[12]	
Study drug (IP) dispensation			X			
Study drug (IP) administration			X	X		
ECG			X[11]	X	X	X
Vital signs			X[11]		X	X
Concomitant medications			X[11]	X	X	X
Adverse events			X[16]	X	X	X
Serious adverse events	X[17]		X	X	X	X
Potassium[6, 13]	X[2]		X[4]	X[5]	X[9]	X[9]
Clinical chemistry[1,6]			X[11]		X	X
Hematology[1,6]			X[11]		X	X
Urinalysis [1,6]			X[11]		X	X
Urine HCG			X[7,11]			X[7]
IP Reconciliation						X

1. Parameters to be measured are detailed in Table 3.
2. Blood potassium will be measured only by i-STAT at the Pre-screening visit (Visit 1).
3. Pre-screening visit is optional. Patients who meet all Pre-screening inclusion/exclusion criteria will be entered into the screening part of the study within 7 days.
4. Potassium will be measured twice 60 (±10) minutes apart within 1 day of first dose administration on the open-label initial phase Day 1(Visit 3) and at 1,2 and 4 hours (±15 min) after administration of the first dose of ZS. Potassium will be measured again at 90 minutes (±15 min) after taking the second dose for patients with i-STAT potassium ≥ 6.1 mmol/L or < 4.0 mmol/L4 hour after the first dose.

5. Potassium will be measured predose (0 hour) and 1 hour (±15 min) after the first dose on the open-label initial phase Day 2 (Visit 4). Patients achieving normokalemia (3.5 to 5.0 mmol/L, inclusive) based on the predose potassium value will skip the Visit 4 and will continue on the same day to the Randomization Visit procedures.
6. Serum clinical chemistry, including S-K, hematology and urinalysis will be measured fasting (nothing by mouth except water only for a minimum of 8 hours prior to collection). On the open-label initial phase Day 1(Visit 3), the Central Laboratory clinical chemistry and hematology samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample.
7. For women of childbearing potential, urine-HCG will be measured at clinic, using the tube provided by Central Laboratory.
8. For patients who achieve normokalemia (3.5 to 5.0 mmol/L, inclusive) based on the predose i-STAT potassium value for open-label initial phase Day 2, will proceed to the Randomization Visit. For patients with i-STAT potassium values >5.0 mmol/L, they will continue on with the remaining procedures.
9. Central laboratory S-K sample collected as part of the serum clinical chemistry.
10. EOS in the open-label initial phase only for patients NOT entering the 28-day randomized treatment study phase, and occurs 7±1 day after the last administration of IP.
11. Baseline parameters should be measured/collected up to 1 day prior to administration of the 1st dose of study drug on the open-label initial phase Day 1(Visit 3).
12. If patient achieves normokalemia (3.5 to 5.0 mmol/L, inclusive) based on the predose potassium value of open-label initial phase Day 2 or Day 3, access IVRS/IWRS to proceed with the Randomization Visit. If the patient permanently discontinues dosing before the end of the open-label initial phase dosing period, access IVRS/IWRS to register subject as not randomized.
13. For diabetic patients all blood potassium samples should be collected prior to insulin administration whenever possible.
14. Study Day in Table 1 is for the open-label initial phase.
15. A complete physical examination should be performed within 1 day prior to administration the first dose of study drug on the open-label initial phase Day 1, and targeted physical examination will be conducted on the open-label initial phase Day 3 and 9 for patients not entering the 28-day randomized treatment study phase. Please refer to Section 5.2.2.
16. AEs will be collected after the patient has signed the main study informed consent, so during the Day 1 (Visit 3), investigator need to check if any AE happened since from main study inform consent.
17. Only SAEs will be collected after the patient has singed the optional Pre-screening informed consent.
18. The defined wider visit window can be applied, if patients are not able to strictly follow the pre-specified visit schedules, due to a prolonged public holiday.

Table 2 Study Plan detailing the procedures: 28-day randomized treatment study phase

Study Visit	**Rand. Visit**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**EOS [9]**
28-day randomized treatment study phase Day[7]	**Day 1[12]**	**Day 2[12]**	**Day 5[12]**	**Day 8[12]**	**Day 12[12]**	**Day 15[12]**	**Day 19[12]**	**Day 22[12]**	**Day 26[12]**	**Day 29[12]**	**Day 35[12]**
Accepted visit window during prolonged public holidays[8]			**Day 3-6**	**Day 7-9**	**Day 10-13**	**Day 14-17**	**Day 18-20**	**Day 21-24**	**Day 25-27**	**Day 28-31**	**Day 32-43**
Eligibility criteria	X										
Physical exam including weight[3, 13]	X					X				X	X
Access IVRS/IWRS[10]	X			X		X		X			
Study drug (IP) dispensation[11]	X			X		X		X			
Study drug (IP) administration[4]	X	X	X	X	X	X	X	X	X		
ECG[3]	X			X		X		X		X	X
Vital signs[3]	X					X				X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events (including SAEs)	X	X	X	X	X	X	X	X	X	X	X
Potassium[6]	X[2]	X	X	X	X	X[2]	X	X	X	X[2]	X[2]
Clinical chemistry[1,3]	X					X				X	X
Hematology[1,3]	X					X				X	X
Urinalysis [1,3]	X					X				X	X
Urine HCG											X[5]
IP Reconciliation										X	

1. Parameters to be measured are detailed in Table 3.
2. Potassium will be measured fasting prior to the 1st daily dose as part of the clinical chemistry panel on Day 1, 15, 29, 35 in the 28-day randomized treatment study phase.
3. Physical Exam, ECG, Vital signs, weight, urinalysis, clinical chemistry including S-Aldo and P-Renin, and hematology parameters will be measured fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic); On the 28-day randomized treatment study phase Days 1,15, 29, and 35(EOS), blood sample which including S-Aldo and P-Renin test need to be collected prior to 10am after the patient has been upright for at least 2 hours and before the ECG.
4. Study drug will be administrated in the clinic on Day 1,2,5,8,12,15,19,22 and 26. If a patient develops i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive (confirmed by taking a second potassium

measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug adjustment rule), dosing will be reduced from qd to every other day for the remainder of the study.

5. For women of Childbearing potential, using-HCG will be measured at clinic, using the tube provided by Central Laboratory.
6. All potassium samples are analyzed by i-STAT and by the Central Laboratory on all occasion. And haemolysed samples should not be sent to the Central Lab for potassium, the sample should be re-drawn to obtain a sample showing no haemolysis. For diabetic patients all blood potassium samples should be collected prior to insulin administration whenever possible.
7. If a scheduled clinic visit falls on a weekend or short public holiday during the 28-day randomized treatment study phase, the scheduled visit may take place either 1 day early or 1 day late (i.e., within±24 hours of the scheduled day) for the 28-day randomized treatment study phase Days 5, 8, 12, 15, 19, 22, 26 and 35, up to 2 days late for the 28-day randomized treatment study phase Day 2 or 2 days early for Day 29. If the Day 29 visit is conducted early, the patient must take IP through Day 28 per protocol.
8. The defined wider visit window can be applied, if patients, are not able to strictly follow the pre-specified visit schedules, due to a prolonged public holiday. If the wider visit windows are applied for a particular visit, it is important that visits before and after such a visit also follows the wider visit windows. This will only apply during prolonged public holidays. Patients are expected to follow the pre-specified visit schedule once the prolonged holiday period is over.
9. EOS occurs 7±1 day after the last administration of IP.
10. Access IVRS/IWRS on visit indicated or if patient permanently discontinues dosing before the end of the 28-day randomized treatment study phase.
11. Due to a public holiday, patients may visit the clinic up to two days after the pre-specified visit schedules, the site investigator can access the IVRS/IWRS in an earlier visit; and the system will assign the patient a new 28-day randomized treatment study phase IP kit containing an additional 7-day supply of IP.
12. Study Day in Table 2 is for the 28-day randomized treatment study phase.
13. Targeted physical examination will be conducted on Days 1, 15, 29, and Day 35 (EOS) during the 28-day randomized treatment study phase, please refer to Section 5.2.2.

4.1 Optional Pre-screening period (Visit 1)

The Pre-screening visit is optional. Study procedures will be performed according to the Study Plan in Table 1.

At Pre-screening, the consenting patients are assessed to ensure that they meet eligibility criteria for the optional Pre-screening part of the study. Patients who do not meet these criteria must not be entered in the optional Pre-screening part of the study.

- Review and confirm the patient's eligibility for the optional Pre-screening part of the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- One potassium sample will be assessed using i-STAT.
- If i-STAT potassium value is <5.1 mmol/L the patient will be declared a pre-screen failure and discontinue from the study. There is no limit to the number of pre-screenings a patient can take part in.
- Record SAEs

Note: Patients who meet all optional Pre-screening inclusion/exclusion criteria and i-STAT potassium value is ≥5.1 mmol/L will be entered into the screening part of the study within 7 days.

4.2 Enrolment/screening period (Visit 2)

Study procedures will be performed according to the Study Plan in Table 1.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be entered in the study.

Patients can be re-screened once during the clinical trial period. A new ICF does not need to be signed before re-screening if the original ICF was signed within 30 days and has not been revised.

After a patient has signed the ICF for the screening part of the study at Visit 2 the site investigator will use the IVRS/IWRS to obtain a unique patient enrolment number after collecting the demographic parameters from the patient (including sex, date of birth, race, ethnic group).

4.3 Treatment Period

Table 1 and Table 2 provide an overview of the procedures performed at each visit during the treatment period, and further details are provided below. Changing the order of the procedures at a visit, e.g., for logistical reasons, would not constitute a protocol violation if agreed in advance and in writing between the site and the sponsor study physician.

4.3.1 Open-label initial phase Day 1 (Visit 3)

Patients will arrive in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic).

The following assessment will be performed:

- Review and confirm the patient's eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2.
- Two potassium samples for assessment, using both i-STAT and the Central Laboratory, will be collected 60 minutes (± 10 min) apart.
- If either i-STAT potassium value is <5.1 mmol/L the patient will be declared a screen failure and withdrawn from the study.
- If both i-STAT values are ≥5.1 mmol/L the following samples will be collected:
  - A blood sample for standard assessment of hematology and clinical chemistry
  - Urine for standard assessment of urinalysis parameters including a pregnancy test if the patient is a woman of childbearing potential
- Obtain vital signs (pulse rate and blood pressure)
- Patient medical and surgical history including co-morbidities (over previous 6 months) will be obtained with the review of selection criteria
- Perform 12-lead Electrocardiogram (ECG)
- Perform a complete physical examination including weight, see Section 5.2.2;
- Review and record the concomitant medications and AEs/SAEs

Note: The above procedures should be performed within 1 day of the first administration of study drug and before any IP administration.

Patients who meet all inclusion/exclusion criteria will be entered into the trial and the following procedures will take place:

- The site will access the IVRS/IWRS and the system will assign the patient an open-label initial phase IP kit
- The first doses of study IP will be administered as a slurry/suspension in water. The patient will be shown/instructed on how to mix and administer the IP
- 1 hour (± 15 min) after dose administration a blood potassium sample (i-STAT and Central Laboratory) will be collected, following which the patient is allowed to break the fast
- Two additional blood potassium samples (i-STAT and Central Laboratory) will then be taken at 2 and 4 hours (±15 min) after dose administration.

- Patients with i-STAT potassium levels < 6.1 and ≥ 4.0mmol/L at the 4 hour (± 15 minutes) post Dose 1 blood draw will be sent home with instructions on how to take the IP. They will be requested to fill out a dosing schedule card indicating when they took the IP. The patient will return to the clinic the following morning for the open-label initial Phase Day 2 (Visit 4)
- Patients with i-STAT potassium ≥ 6.1 or < 4.0 mmol/L at the 4 hour post Dose 1 blood draw will stay in the clinic and take the second dose of study drug approximately 4-hours after the first dose. They will then remain in the clinic an extra 90 minutes (± 15 minutes) after taking the second dose when another blood sample for potassium determination (i-STAT and Central Laboratory will be collected and an ECG will be recorded).
- If i-STAT potassium levels are > 6.2 mmol/L as determined by the i-STAT at the 90-minute post Dose 2 blood draw, the patient will be discontinued from the study. Patients will return to the clinic 7 (±1) days later for an EOS visit.
- If i-STAT potassium levels are ≤6.2 mmol/L and the ECG does not show any of the ECG withdrawal criteria, the patient will be sent home with the third dose of study drug and the dosing card and return to the clinic in the morning of the open-label initial phase Day 2 (Visit 4).
- See Section 7.2 regarding how to handle patients with potassium < 3.5mmol/L.

4.3.2 Open-label initial phase Day 2 (Visit 4)

Patients will arrive fasting at the clinic in the morning (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium levels will be evaluated by i-STAT and the Central Laboratory. i-STAT potassium measurement will be done during the visit to determine the next steps of procedures.
  - If the i-STAT potassium value is < 3.5mmol/L, see Section 7.2 regarding how to handle patients.
  - If the i-STAT potassium value is between 3.5 and 5.0 mmol/L inclusive the patient will skip the remaining procedures for initial phase Day 2 and will be randomized (on the same day) into the 28-day randomized treatment study phase, and complete the remaining procedures detailed in Section 4.3.4. In this case Visit 4 will be skipped completely and the patient will conduct the Randomization visit instead. No data entry is done in the Visit 4 eCRF.

- If the i-STAT potassium value is ≥ 5.1 mmol/L, the patient will receive an additional 24 hours of ZS 10g TID and the following procedures will be performed.

- An ECG will be performed (Section 5.2.3)
- Following completion of the above procedures, the first daily dose of IP will be administered in the clinic as a slurry/suspension in water, followed by the 1 hour post Dose 1 blood draw (see Figure 4 for the flow chart based on the potassium value), after which the patient is allowed to break the fast.
- Patients will then be sent home with study drug and instructions on how to take the IP. They will be requested to fill out a dosing schedule card indicating when they took the IP.
- Patients will return to the clinic the following morning and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.3 Randomization Visit - For patients not entering the 28-day randomized treatment study phase

On Day 3 of the Open-Label initial phase, patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- Potassium levels will be evaluated by i-STAT and the Central Laboratory.
    - If the i-STAT potassium value is within the normal range (3.5 to 5.0 mmol/L, inclusive) the patient will be randomized into the 28-day randomized treatment study phase and complete the procedures detailed in (Section 4.3.4).
    - However if the i-STAT potassium value is > 5.0 mmol/L or < 3.5 mmol/L the below assessments will be performed:
        - Samples will be collected: Blood samples for the standard assessment of clinical chemistry; blood sample for standard assessment of hematology; Urine for standard assessment of urinalysis parameters
        - An ECG will be performed (Section 5.2.3)
        - Perform physical examination including weight (Section 5.2.2)

- Withdraw the patient from the open-label initial phase and access IVRS/IWRS to register subject as not randomized.

- Patients will then DISCONTINUE from the study medication, and receive standard of care at the discretion and the direction of his/her own physician. However, the patient will need to return to the clinic 7 (± 1) days later for an EOS visit in the morning, fasting, nothing by mouth except water (Section 4.4).

4.3.4 Randomization Visit - For patients entering the 28-day randomized treatment study phase

The Day 1 of the 28-day randomized treatment study phase will take place on the day when the patient achieves an i-STAT potassium value between 3.5 and 5.0 mmol/L, inclusive, after 24 or 48 hours of ZS 10 g TID treatment during the open-label initial phase.

The following assessments will be performed:

- Samples will be collected prior to any IP administration:
  - Blood samples for standard assessment of hematology and clinical chemistry including S-K
  - Urine for standard assessment of urinalysis parameters
- An ECG will be performed (Section 5.2.3).
- A targeted physical examination including weight (Section 5.2.2).
- Site investigator access the IVRS/IWRS and randomize the patient. The system will assign the patient a study IP kit (Week 1) containing a 7-day supply of IP.

  If the 28-day randomized treatment study phase Day 2 visit falls on a public holiday or weekend, the patient should be informed when next to return to the clinic. They will be requested to fill out a dosing schedule card indicating when they took the IP and when they ate breakfast each day and to bring the used and/or unused IP and completed dosing schedule card with them when they return to the clinic.

4.3.5 28-day randomized treatment study phase Day 2 (Visit 6)

If the scheduled 28-day randomized treatment study phase Day 2 clinic visit falls on a weekend or a short public holiday the Day 2 visit (Visit 6) may occur up to 2 days late.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (the 28-day randomized treatment study phase Day 5) and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.6 28-day randomized treatment study phase Day 5 (Visit 7)

Investigator are required to plan each patient's visit schedule in an optimal way and in accordance with the CSP. If patients are not able to accomplish a pre-specified visit during the 28-day randomized treatment study phase, due to a prolonged public holiday, a "wider" visit window can be applied (see Table 2). Patients are expected to follow the pre-specified (tighter visits) visit schedule once the prolonged holiday period is over.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (the 28-day randomized treatment study phase Day 8) and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.7 28-day randomized treatment study phase Day 8 (Visit 8)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Prior to IP administration, potassium samples (i-STAT and Central Laboratory) will be collected

- An ECG will be performed (Section 5.2.3).
- The site will access the IVRS/IWRS. The system will assign the patient a new 28-day randomized treatment study phase IP kit (Week 2) containing an additional 7-day supply of IP.
- Patients will return to the clinic, in the morning, four (4) days later (the 28-day randomized treatment study phase Day 12) and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.8 28-day randomized treatment study phase Day 12 (Visit 9)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (the 28-day randomized treatment study phase Day 15) and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.9 28-day randomized treatment study phase Day 15 (Visit 10)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP sachets and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- The following tests will be performed before any IP administration
  - i-STAT blood potassium assessment
  - Blood samples for a standard assessment of clinical chemistry including, S-K
  - Blood for a standard assessment of hematology parameters
  - Urinalysis parameters

- An ECG will be performed (Section 5.2.3)
- A targeted physical examination will be performed (Section 5.2.2)
- The site will access the IVRS/IWRS. The system will assign the patient a new 28-day randomized treatment study phase IP kit for use in Week 3 containing an additional 7-day supply of IP.
- Patients will return to the clinic, in the morning, four (4) days later (the 28-day randomized treatment study phase Day 19 and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.10 28-day randomized treatment study phase Day 19 (Visit 11)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Potassium samples (i-STAT and Central Laboratory) will be collected prior to any IP administration.
- Patients will return to the clinic, in the morning, three (3) days later (the 28-day randomized treatment study phase Day 22) and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.11 28-day randomized treatment study phase Day 22 (Visit 12)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Blood samples for measurement of potassium (i-STAT and Central Laboratory) will be collected.
- An ECG will be performed (Section 5.2.3)
- The site will access the IVRS/IWRS. The system will assign the patient a new 28-day randomized treatment study phase IP kit (Week 4) containing an additional 7-day supply of IP.

- Patients will return to the clinic, in the morning, four (4) days later (the 28-day randomized treatment study phase Day 26) and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.12 28-day randomized treatment study phase Day 26 (Visit 13)

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Blood samples for measurement of potassium (i-STAT and Central Laboratory) will be collected.
- Patients will return to the clinic, in the morning, three (3) days later (Day 29), fasting, nothing by mouth except water and bring the used and/or unused IP and completed dosing schedule card with them.

4.3.13 28-day randomized treatment study phase Day 29 (Visit 14)

Please note: If the Day 29 visit is conducted early, the patient must take IP through the 28-day randomized treatment study phase Day 28 per protocol. In this instance IP will be administered after all of the Day 29 procedures have been conducted.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic). They will bring the used and/or unused IP, and completed dosing schedule card with them.

The following assessments will be performed:

- The clinic staff will solicit any AEs, note any changes in concomitant medications, examine the returned IP and make note of the time the doses were taken and any unused IP on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- The following tests will be performed:
  - i-STAT blood potassium assessment
  - Blood samples for a standard assessment of clinical chemistry including, S-K
  - Blood for a standard assessment of hematology parameters
  - Urinalysis parameters

- An ECG will be performed (Section 5.2.3)
- A targeted physical examination will be performed (Section 5.2.2)
- Patients will be instructed to return to the clinic, in the morning, 7 ±1 days following the last study IP administration (the 28-day randomized treatment study phase Day 35) for an EOS visit.

4.4 Follow-up period (EOS)

Follow up visit will be performed at Day 9 for the open-label initial phase, and Day 35 for the 28-day randomized treatment study phase, or 7 ±1 days following the last study IP administration for patients who are withdrawn from the study.

Patients will arrive at the clinic in the morning, fasting (nothing by mouth except water for a minimum of 8 hours prior to potassium sample collection at the clinic).

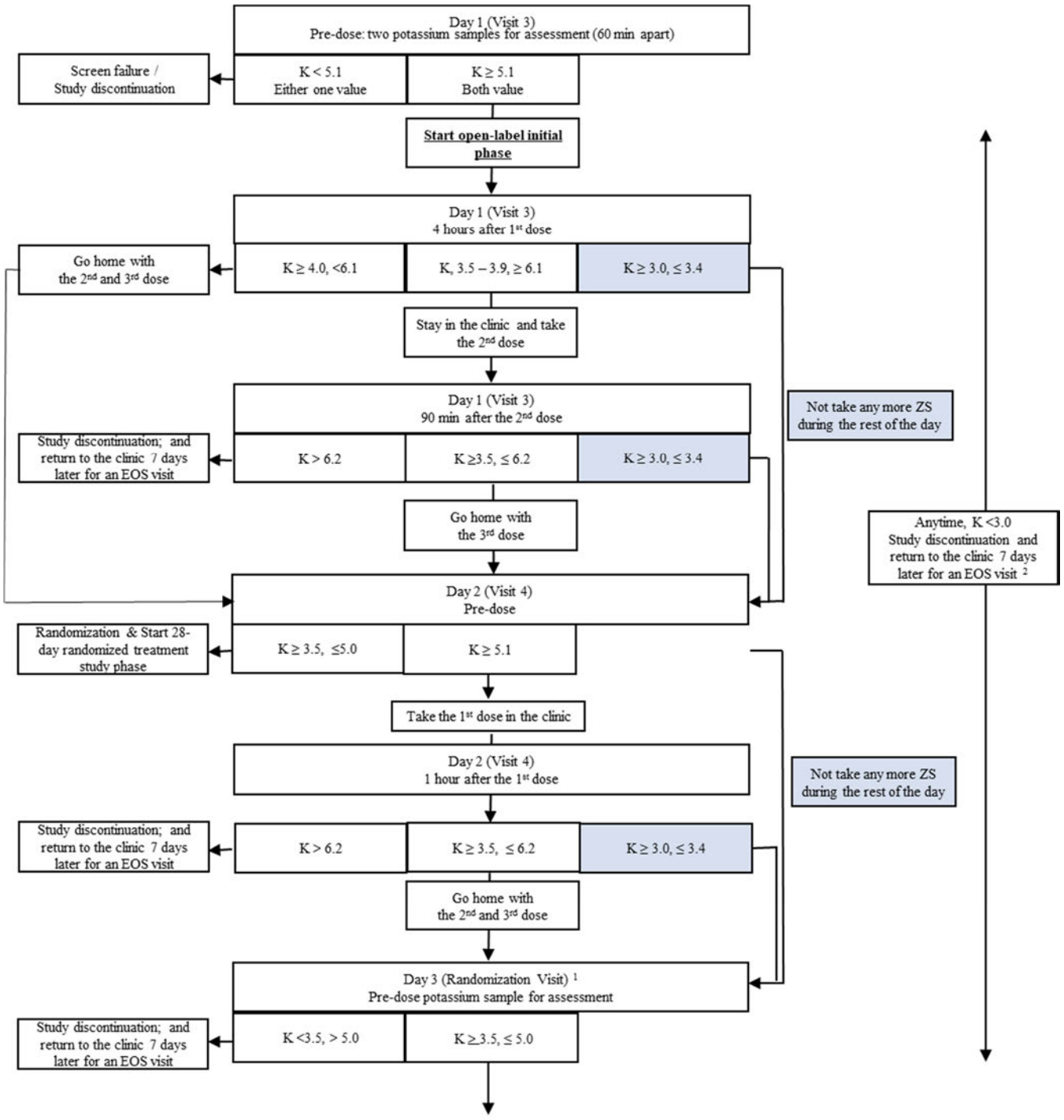
The following assessments will be performed:

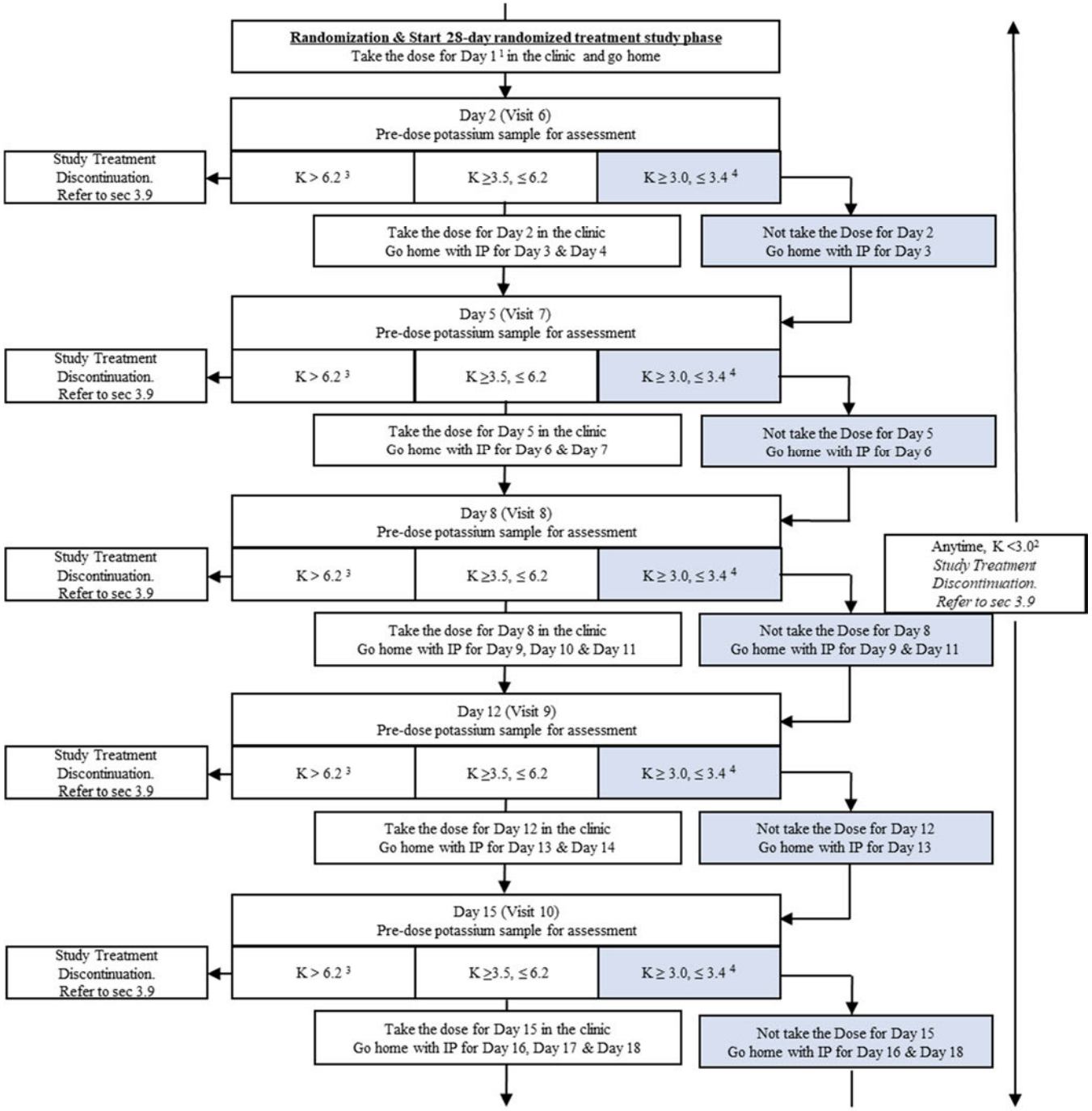
- The clinic staff will solicit any AEs, note any changes in concomitant medications on the eCRF and source documents.
- Vital signs (pulse rate and blood pressure) will be obtained.
- The following tests/procedures will be performed:
  - i-STAT blood potassium assessment
  - Blood samples for a standard assessment of clinical chemistry including, S-K
  - Blood for a standard assessment of hematology parameters
  - Urine for standard urinalysis parameters
  - A pregnancy test if the patient is a woman of childbearing potential
  - An ECG will be performed (Section 5.2.3)
  - A targeted physical examination will be performed (Section 5.2.2)

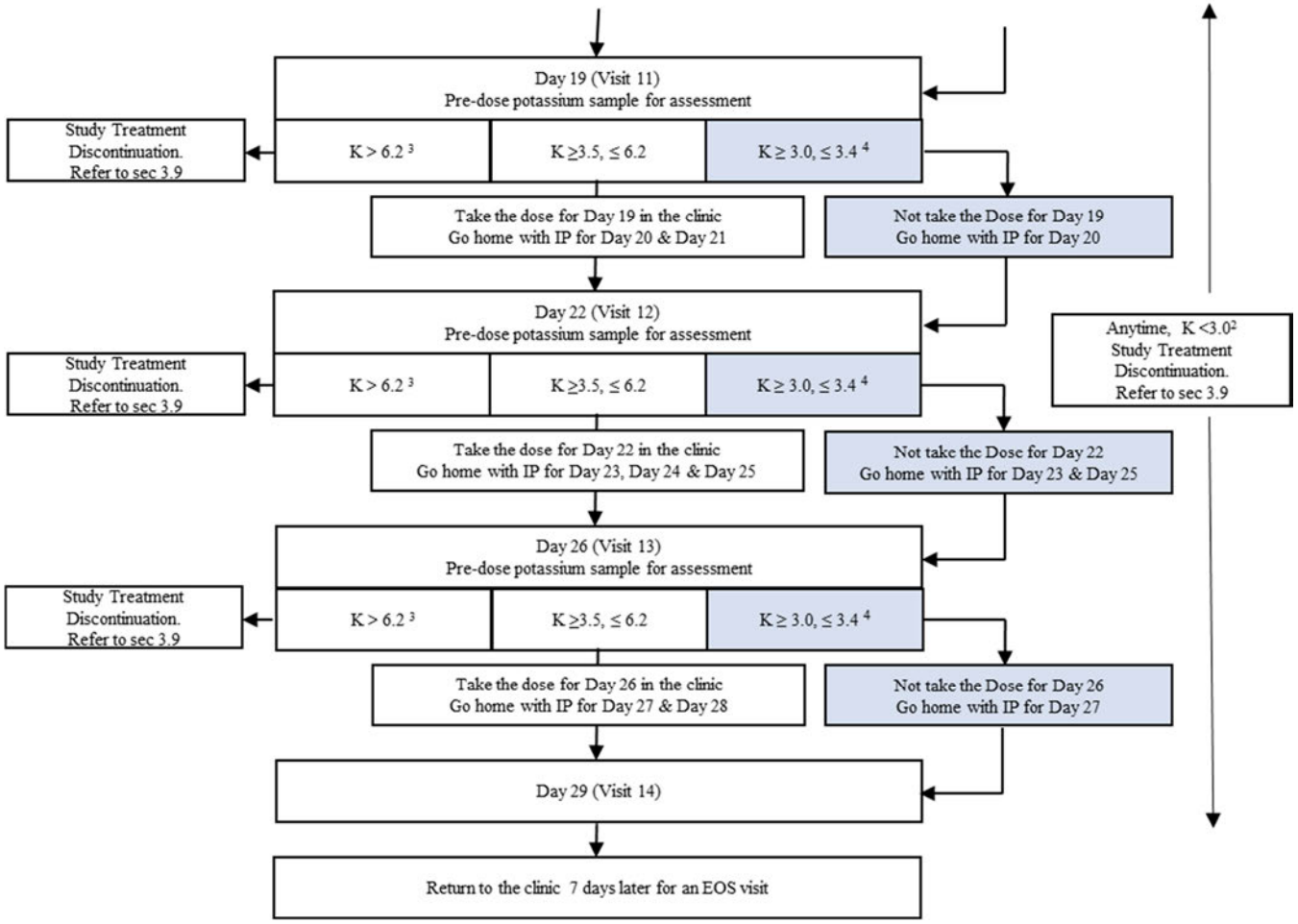
Note: If the EOS for the open-label initial phase or the 28-day randomized treatment study phase falls on a weekend or a short public holiday, the EOS visit can be performed either on the preceding Friday or the following Monday.

If the EOS for the open-label initial phase falls on a prolonged public holidays, the EOS visit can be performed from Study Day 4 to Study Day 16. If the EOS for the 28-day randomized treatment study phase falls on a prolonged public holidays, the EOS visit can be performed from Study Day 32 to Study Day 43. This will only apply during prolonged public holidays.

Figure 4 Flow chart based on the Potassium level, which will be measured by i-STAT




Randomization & Start 28-day randomized treatment study phase
Take the dose for Day 1 [1] in the clinic and go home
Day 2 (Visit 6)
Pre-dose potassium sample for assessment
K > 6.2 [3]
K ≥3.5, ≤ 6.2
K ≥ 3.0, ≤ 3.4 [4]
Study Treatment Discontinuation. Refer to sec 3.9
Take the dose for Day 2 in the clinic
Go home with IP for Day 3 & Day 4
Not take the Dose for Day 2
Go home with IP for Day 3
Day 5 (Visit 7)
Pre-dose potassium sample for assessment
Study Treatment Discontinuation. Refer to sec 3.9
K > 6.2 [3]
K ≥3.5, ≤ 6.2
K ≥ 3.0, ≤ 3.4 [4]
Take the dose for Day 5 in the clinic
Go home with IP for Day 6 & Day 7
Not take the Dose for Day 5
Go home with IP for Day 6
Day 8 (Visit 8)
Pre-dose potassium sample for assessment
Study Treatment Discontinuation. Refer to sec 3.9
K > 6.2 [3]
K ≥3.5, ≤ 6.2
K ≥ 3.0, ≤ 3.4 [4]
Anytime, K <3.0 [2]
Study Treatment Discontinuation. Refer to sec 3.9
Take the dose for Day 8 in the clinic
Go home with IP for Day 9, Day 10 & Day 11
Not take the Dose for Day 8
Go home with IP for Day 9 & Day 11
Day 12 (Visit 9)
Pre-dose potassium sample for assessment
Study Treatment Discontinuation. Refer to sec 3.9
K > 6.2 [3]
K ≥3.5, ≤ 6.2
K ≥ 3.0, ≤ 3.4 [4]
Take the dose for Day 12 in the clinic
Go home with IP for Day 13 & Day 14
Not take the Dose for Day 12
Go home with IP for Day 13
Day 15 (Visit 10)
Pre-dose potassium sample for assessment
Study Treatment Discontinuation. Refer to sec 3.9
K > 6.2 [3]
K ≥3.5, ≤ 6.2
K ≥ 3.0, ≤ 3.4 [4]
Take the dose for Day 15 in the clinic
Go home with IP for Day 16, Day 17 & Day 18
Not take the Dose for Day 15
Go home with IP for Day 16 & Day 18



1. The open-label initial phase Day 3 is also the same day as the Randomization Visit (Day 1) of the 28-day randomized treatment study phase. Patients achieving normokalemia in the morning of the open-label initial phase Day 2 will enter the Study Day 1 of the 28-day randomized treatment study phase directly.
2. Patient with confirmed i-STAT potassium value <3.0 mmol/L at any time during the study (confirmed by taking a second potassium measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug discontinuation rule). Patients discontinuing due to this criterion must immediately receive appropriate medical treatment to manage their hypokalemia.
3. Patient with confirmed i-STAT potassium value >6.2 mmol/L during the 28-day randomized treatment study phase (confirmed by taking a second potassium measurement after a 10 ± 2-minute interval, and both i-STAT values meet the study drug discontinuation rule). Patients discontinuing due to this criterion must immediately receive appropriate medical treatment to manage their hyperkalemia.
4. Patient with confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval), during the 28-day randomized treatment study phase, dosing will be reduced from qd to qod for the remainder of the study.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Blood potassium

Blood samples for determination of potassium will be taken at the times indicated in the Study Plan (see Table 1 and Table 2). Potassium samples will be analyzed locally using i-STAT devices, and serum samples will be prepared and shipped to Central Laboratory. All serum samples should be examined and any hemolyzed samples MUST be redrawn. In the event that hemolysis or other artefacts are suspected based on the reported i-STAT result the sample may be re-drawn to confirm the result. Only the confirmatory sample result needs to be reported in the eCRF.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1 and Table 2). 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 in the appropriate eCRF module.

The clinical chemistry, hematology and urinalysis will be performed at a central laboratory.

Table 3 Laboratory Safety Variables

Haematology	**Clinical Chemistry (serum)**
B-Hemoglobin (Hb)	S-Total Protein
B-Hematocrit	S-Albumin
B-Erythocyte count (RBC)	S-Bicarbonate
B-Total leukocyte count (WBC)	S-Blood Urea Nitrogen
B-Leukocyte differential count (absolute count)	S-Creatinine
B-Platelet count	S-Bilirubin, total
	S-Alkaline phosphatise (ALP)
Urinalysis	S-Glucose
U-PH	S-Sodium
U-Specific gravity	S-Potassium[1]
U-Glucose	S-Inorganic phosphate
U-Ketones	S-Calcium, total
U-Bilirubin	S-Magnesium
U-Urobilinogen	S-Gamma-glutamyl transferase (GGT)
U-Blood	S-Aspartate transaminase (AST)
	S-Alanine transaminase (ALT)
U- Human chorionic gonadotropin (HCG) (only for females of childbearing potential) [2]	S-Aldosterone[3]
	P-Renin [3]

1. Blood potassium will be measured only by i-STAT at the optional Pre-screening visit. Blood potassium will be measured by i-STAT and Serum potassium will be measured by C-lab for Visit 2 to EOS Visit.
2. Urine-HCG will be measured at clinic, used the tube provided by Central Laboratory.
3. Patients need to be either standing or seated upright for at least 2 hours before sample collection for S-Aldosterone and P-Renin assessment.

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 center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

Blood chemistry and hematology parameters will be evaluated fasting, by the Central Laboratory, on the open-label initial phase Days 1 for all patients, 3 and 9 (EOS visit) for

patients NOT entering the double-blind 28-day randomized treatment study phase and on the 28-day randomized treatment study phase Days 1, 15, 29 and 35 (EOS).

S-K will be evaluated as part of the clinical chemistry sample on the open-label initial phase Day 1 (60 minute baseline sample), the open-label initial phase Days 3 and 9 (EOS) for patients not entering the 28-day randomized treatment study phase, and on the 28-day randomized treatment study phase Days 1,15, 29 and 35 (EOS).

Urine samples will also be collected during the study. The open-label initial phase Day 1 urine pregnancy test for women of childbearing potential is performed as part of the screening procedure prior to any IP administration and is repeated at the last visit of the study, either on the open-label initial phase Day 9, or on the 28-day randomized treatment study phase Day 35.

Urinalysis, will be performed by the Central Laboratory at the open-label initial phase Day 1 for all patients and on the open-label initial phase Days 3 and 9 for patients NOT entering the 28-day randomized treatment study phase, and on the 28-day randomized treatment study phase Days 1, 15, 29 and the 28-day randomized treatment study phase Day 35 (EOS).

Note: Whenever possible, all blood draws collected prior to meals should be collected prior to insulin/insulin analog treatment.

5.2.2 Physical assessments

A complete physical examination should be performed within 1 day of administering the first dose of study drug on the open-label initial phase Day 1 (Baseline: all patients), and targeted physical examination will be conducted on the open-label initial phase Day 3 for all patients and on Day 9 for patients not entering the 28-day randomized treatment study phase. During the 28-day randomized treatment study phase, targeted physical examination will be conducted on Days 1, 15, 29, and 35 (EOS).

The complete physical examination includes the following: general appearance including skin, height and weight, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular including assessment of signs of heart failure, lungs, abdomen, and neurological systems.

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

5.2.3 ECG

A 12-lead ECG will be performed after the patients has been lying down for 5 minutes at the times indicated in the Study Plan in Table 1 and Table 2. Heart rate, P and QRS durations, PR and QTc(f) intervals will be recorded from standard lead of the computerized quantitative 12-lead ECG.

ECGs will be recorded at the open-label initial phase Day 1, Day 2, the open-label initial phase Day 3 and Day 9 (EOS) for patients NOT entering the double-blind 28-day randomized

treatment study phase, and on the 28-day randomized treatment study phase Days 1, 8, 15, 22, 29, and 35 (EOS). When applicable ECGs will be performed after the S-Aldo and P-Renin samples are drawn and before the first daily dose of IP.

In addition, for patients who have i-STAT potassium levels ≥ 6.1 mmol/L or < 4.0 but ≥3.5 mmol/L at the 4 hour post 1st dose time point on the open-label initial phase Day 1, an additional ECG will be recorded 1.5 hours post 2nd dose. Patient who develops severe hypokalemia (i-STAT potassium values <3.0 mmol/L) at any time during the study or > 6.2 mmol/L during the 28-day randomized treatment study phase, an additional ECG will need to be performed.

Study subjects with pacemakers:

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

5.2.4 Vital signs

5.2.4.1 Pulse rate and blood pressure

Pulse rate and systolic and diastolic blood pressure (BP) will be assessed using non-invasive equipment by an adequately trained health care professional. Measurements with a calibrated sphygmomanometer are preferred. If not available, another device calibrated carefully in proportion to a mercury sphygmomanometer is preferred. Use of aneroid manometers should be avoided. Appropriate cuff size must be used to ensure accurate measurement.

The disappearance of sound (Korotkov phase V) should be used for the diastolic reading. Three (3) readings separated by 2 minutes should be averaged, and the average result will be recorded in the eCRF. If the first two readings of SBP differ by more than 5 mmHg, additional readings should be obtained. Blood pressure should be checked in both arms at visit 3. Subsequent blood pressure measurements should be recorded in the arm with the higher pressure. Blood pressure should be measured in either supine or sitting position. No shift from one position to another should be made during the study. Supine or sitting posture should be adopted for at least 5 minutes before measurement. The patient should be relaxed and with the arm outstretched and supported. Blood pressure should be measured under standardized conditions, as nearly as possible at the same time each visit, on the same arm, by the same personnel, and with the same apparatus.

5.3 Other assessments (Not applicable)

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Genetics (Not applicable)

5.7 Biomarker analysis (Not applicable)

5.8 Storage, re-use and destruction of biological samples

After the analyses are complete the samples will be either completely consumed during the analytical process or disposed of after the analysis.

5.9 Labeling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

5.10 Volume of blood

The total volume of blood that will be drawn from each patient for this study is listed in Table 4 and Table 5 as below. The collection of additional samples is performed locally at the discretion of the investigator and recorded in the eCRF as appropriate, thus requiring additional sample volumes.

Table 4 Volume of blood to be withdrawn from each patient: optional pre-screening and open-label initial phase

Assessment	Sample Volume (mL)	Number of Samples					Maximum blood volume Total (mL)
		V1	V 3 (D 1[7])	V 4 (D 2[7])	Rand (D 2/3[7,8])	EOS (D 9[7])	
Hematology	2		1[3]		0-1[5]	1	6
Clinical Chemistry	8.5		1[3,6]		0-1[5,6]	1[6]	25.5
Potassium (Central Lab S-K)	2.5		4-5[2,6]	2[4]			17.5

Table 4 Volume of blood to be withdrawn from each patient: optional pre-screening and open-label initial phase

Assessment	Sample Volume (mL)	Number of Samples					Maximum blood volume Total (mL)
		V1	V 3 (D 1[7])	V 4 (D 2[7])	Rand (D 2/3[7,8])	EOS (D 9[7])	
Potassium (i-STAT)	1	1[1]	5-6[2]	2[4]	1	1	11
Maximum Blood Volume Total (mL)		**1**	**29**	**7**	**11.5**	**11.5**	**60**

V= Visit; D=Day

1. Blood potassium will be measured only by i-STAT at the optional Pre-screening visit (Visit 1).
2. Potassium will be measured twice 60 (±10) minutes apart within 1 day of first dose administration on the open-label initial phase Day 1(Visit 3) and at 1,2 and 4 hours (±15 min) after administration of the first dose of ZS; An extra potassium will be measured at 90 minutes (±15 minutes) after taking the second dose for patients with i-STAT potassium ≥ 6.1 or < 4.0 mmol/L at the 4 hour post Dose 1.
3. On the open-label initial phase Day 1(Visit 3), the Central Laboratory clinical chemistry and hematology samples will be collected at the same time as the 60 minutes i-STAT screening potassium sample.
4. Potassium will be measured predose (0 hour) and 1 hour (±15 min) post 1st dose on the open-label initial phase Day 2 (Visit 4), for those achieving normokalemia based on the predose i-STAT potassium value, they will then enter the randomized phase directly.
5. Clinical chemistry and hematology samples only for patients with i-STAT potassium values >5.0 mmol/L as measured fasting on the open-label initial phase Day 3.
6. Central laboratory S-K sample collected as part of the serum clinical chemistry
7. Study Day in Table 4 is day for the open-label initial phase.
8. Randomization Visit may occur for patients who achieve normokalemia on open-label initial phase Day 2 or 3.

Table 5 Volume of blood to be withdrawn from each patient: 28-day randomized treatment study phase

Assessment	Sample Volume (mL)	Number of Samples											Maximum blood volume Total (mL)
		Rand D1[2]	V6 D2[2]	V7 D5[2]	V8 D8[2]	V9 D12[2]	V10 D15[2]	V11 D19[2]	V12 D22[2]	V13 D26[2]	V14 D29[2]	EOS D35[2]	
Hematology	2	1					1				1	1	**8**
Clinical Chemistry	8.5	1[1]					1[1]				1[1]	1[1]	**34**

Table 5 Volume of blood to be withdrawn from each patient: 28-day randomized treatment study phase

Assessment	Sample Volume (mL)	Number of Samples											Maximum blood volume Total (mL)
		Rand D1[2]	V6 D2[2]	V7 D5[2]	V8 D8[2]	V9 D12[2]	V10 D15[2]	V11 D19[2]	V12 D22[2]	V13 D26[2]	V14 D29[2]	EOS D35[2]	
Potassium (Central Lab S-K[1])	2.5		1	1	1	1		1	1	1			**17.5**
Potassium (i-STAT)	1	1	1	1	1	1	1	1	1	1	1	1	**11**
Maximum Blood Volume Total (mL)		**11.5**	**3.5**	**3.5**	**3.5**	**3.5**	**11.5**	**3.5**	**3.5**	**3.5**	**11.5**	**11.5**	**70.5**

V=Visit; D=Day

1. Potassium will be measured fasting prior to the daily dose. Central Laboratory S-K sample collected as part of the serum clinical chemistry at Day 1, 15, 29, and 35.
2. Study Day in Table 5 is day for the 28-day randomized treatment study phase.

5.11 Guidance related to assessments, and procedures during COVID-19 pandemic

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase, 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/incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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

For further guidance on the definition of a SAE, see Appendix A to Clinical Study Protocol

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from the time of main study informed consent, throughout the treatment period and including the EOS visit. SAEs will be collected from the time of optional Pre-screening informed consent, throughout the treatment period and including the EOS visit.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment (EOS) or other assessment/visit as appropriate 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE:

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE 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)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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 a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit?', 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.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised 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 or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign

will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

6.5 Overdose

ZS has been given to patients at doses of up to 30 g per day for 1 to 3 days and up to 15 g per day for 11 months. For the purpose of this study, during the open-label initial phase, any ZS dose greater than 30g within one day, or continuity of the correcting dose (10g TID) for more than 72 hours will be considered an overdose; during the randomized treatment phase, a dose higher than 15g/day will be considered an overdose. At any time during the study, doses higher than 15g taken at once will be considered an overdose.

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient 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 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

When the CRF module is used include the following: The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Nonclinical data with ZS-9 based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and toxicity to reproduction and development did not reveal special hazard effect on libido, fertility, or embryofetal and postnatal development (see IB for further details). Therefore there is no restriction on fathering children or donating sperm during the study.

In case of pregnancy of the patient's partners, an ICF FOR PREGNANT PARTNERS OF STUDY PATIENTS the partner's pregnancy will be sent to the partner to obtain her consent for collection of pregnancy information. Such pregnancy report will follow the same timeframe and routing as described for any participant's pregnancy. These pregnancies will be also followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be obtained and documented if possible.

6.7 Medication Error

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

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 subject.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the subject 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 e.g. medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature

- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (excluding IVRS/IWRS errors)

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

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product and strength	**Dosage form**	**Manufacturer**
Sodium Zirconium Cyclosilicate (ZS) 5g	Powder for Oral Suspension in a sachet	AstraZeneca
Sodium Zirconium Cyclosilicate (ZS) 10g	Powder for Oral Suspension in a sachet	AstraZeneca
Placebo	Powder for Oral Suspension in a sachet	AstraZeneca

7.2 Dose and treatment regimens

During the open-label initial phase all patients will receive ZS per os (PO) at a dose of 10g three times a day (tid) for a maximum of 6 doses, study drug will be administered orally before breakfast on the open-label initial phase Days 1 and 2, but for other dose during the open-label initial phase, study drug will be administrated orally with or without food. The individual kit will be assigned through IVRS/IWRS.

For patients with i-STAT potassium values within the normokalemic range (3.5 to 5.0 mmol/L, inclusive) in the morning of the open-label initial phase Day 2 or Day 3, the site will contact IVRS/IWRS 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 IVRS/IWRS 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.

If a patient develops confirmed i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive, during the open-label initial phase the patient will be directed to not take any more ZS during the rest of that day and return the next day to continue the therapy in the study. E.g. patients with potassium values between 3.0 mmol/L and 3.4 mmol/L on Day 2 will not take the rest of the doses on Day 2, and will return fasting to be assessed for randomization into the 28-day randomized treatment study phase on Day 3. Patients with potassium values between 3.0 mmol/L and 3.4mmol/L already on Day 1 will not take the rest of the doses on Day 1, and will return fasting to have their potassium tested again on Day 2. If the potassium on Day 2 is between 3.5 and 5.0mmol/L then the patient will be randomized into the 28-day randomized treatment study phase. If the potassium value is >=5.1mmol/L then the patient will continue their therapy as per the study schedule. If the potassium remains low (≤3.4 mmol/L but not <3.0 mmol/L) on Day 2, the Day 2 doses should not be taken and the patient will return fasting to be assessed for randomization into the 28-day randomized treatment study phase on Day 3, and only normokalemic patients (potassium between 3.5 - 5.0 mmol/L, inclusive) will be randomized.

If a patient develops i-STAT potassium values between 3.0 mmol/L and 3.4 mmol/L, inclusive (confirmed by taking a second potassium measurement after a 10 ± 2 minute interval), during the 28-day randomized treatment study phase, dosing will be reduced from qd to qod for the remainder of the study.

Patients with confirmed potassium <3.0 mmol/L in both study phases should discontinue from therapy as per Section 3.9.

Patients with confirmed i-STAT potassium >6.2 mmol/L during the 28-day randomized treatment study phase should discontinue from therapy as per Section 3.9.

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

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drug should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The designated individual (e.g., Pharmacist) will account for all study drugs dispensed to and returned from the patient.

IP kits will be uniquely coded and assigned through the randomization and subsequent visits via the IVRS/IWRS. On receipt of IP supplies the Investigator/designee will check the supplies against the shipment manifest and will confirm receipt of IP shipments via the IVRS/IWRS. The system will then issue an acknowledgement receipt. Sites are required to place all shipment manifests and acknowledgement receipts in the site regulatory binder.

The designated individual (e.g., pharmacist) is also responsible for maintaining accurate records accounting for the receipt, dispensing and final disposition of all investigational products using the appropriate IP logs provided by AstraZeneca.

7.7 Concomitant and other treatments

All concomitant medications taken by the patient from 7 days prior to the open-label initial phase Day 1 until the 28-day randomized treatment study phase Day 35(EOS), or the end of the study (7 ± 1 days after the last dose of IP) for patients, will be recorded.

Whenever possible, all blood draws collected prior to meals should be collected prior to any insulin/insulin analog treatment. From the open-label initial phase Day 1 through the 28-day randomized treatment study phase Day 28, the time of dosing with insulin/insulin analogs must be recorded when IP is administered in the clinic.

During the study, the patient cannot receive alternative treatment for hyperkalemia while taking IP. If dosing with IP is discontinued or the patient has completed dosing, the patient may receive alternative treatment for hyperkalemia if clinically indicated prior to completing the EOS visit. Any alternative treatment administered after the end of IP administration and prior to the EOS visit must be recorded in the concomitant medication eCRF page (and as AE if applicable).

In addition to therapies for hyperkalemia also other drugs with World Health Organization Anatomic Therapeutic Chemical classification code V03AE, i.e., potassium binders such as sevelamer, calcium acetate, and lanthanum carbonate, are prohibited to be taken while receiving IP, as the effects of potassium binding drugs may effect safety laboratory assessments.

Changes to RAAS inhibitor and/or diuretics (including adding a new, changing the dose or discontinuation or switching of RAAS inhibitor and/or diuretics) during the study are prohibited. If clinically indicated to change the RAAS inhibitor and/or diuretics, the patients should discontinue study medication.

7.7.1 Other concomitant treatment

When co-administered with ZS, some oral medications with gastric pH-dependent bioavailability may exhibit a clinically meaningful increase or decrease in their bioavailability. Therefore, these drugs should be administered at least 2 hours before or 2 hours after study drug to mitigate the risk of drug interactions.

Drugs that should be taken 2 hours before or after study drug to avoid a possible raised gastric pH drug interaction are listed below:

Class of Drug	**Drugs**
Azole antifungals	Ketoconazole, Itraconazole, Posaconazole, Voriconazole
Anti-HIV drugs	Atazanavir, Nelfinavir, Indinavir, Ritonavir, Saquinavir, Raltegravir, Ledipasvir, Rilpivirine
Tyrosine kinase inhibitors	Erlotinib, Dasatinib, Nilotinib

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

7.8 Post Study Access to Study Treatment (Not Applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis and conduct of the study will remain blinded until protocol violators have been identified, and the study database is locked. Analysis will be performed by AstraZeneca or its representatives.

A detailed Statistical Analysis Plan (SAP) will be finalized prior to Database Lock.

8.2 Sample size estimate

The sample size is determined to detect a clinically meaningful difference in the primary endpoint of the mean S-K during the 28-day randomized treatment study phase Study Days 8-29 between each active dose (high to low) vs. placebo control. Assuming an inter-subject standard deviation of 0.50, approximately 250 patients, (100 patients per active dose treatment arm and 50 patients for placebo control arm), will provide >90% power to detect a mean difference of 0.30 in mean S-K during Study Days 8-29, comparing each active dose (high to low) vs. placebo control using a two-sided t-test at a significance level of 5%. Assuming 90% of patients will be normokalemic after treatment in the open label initial phase (see Section 7.2), approximately 280 patients will be needed to enter the open-label initial phase.

The power and sample size is determine based on the number of patients required to evaluate the primary hypothesis of the study. However, in the testing sequence presented in Table 6, the open-label initial phase mean change from baseline of S-K 48 hours after first dose of ZS 10g will be evaluated first. A sample size of 280 patients will provide >99% power to detect a more than 18% relative reduction (i.e., 1.05 absolute reduction) in mean change from baseline of S-K 48 hours after the first dose of ZS 10g during the open-label treatment initial phase.

The assumptions used in the above sample size estimations are taken from the ZS-004 study.

8.3 Definitions of analysis sets

Unless otherwise specified, all efficacy analyses will be performed using the full analysis set (FAS), which is based on the Intent-to-Treat (ITT) principle. That is, patients allocated to a treatment group will be followed up, assessed, and analysed as members of that group irrespective of their compliance with the planned course of treatment.

The FAS includes all randomized patients. Patients without any post randomization data will not be used in any of the analyses, but will be accounted for in summary statistics tables. Explicit definitions are presented in Section 8.3.1 below.

8.3.1 Full analysis sets (FAS)

FAS-OLP: For the open-label initial phase, the full analysis set will include all patients registered in the open-label initial phase.

FAS-RTP: For the 28-day randomized treatment study phase, the full analysis set will include all patients who are randomized to the 28-day randomized treatment study phase.

Unless otherwise specified, all efficacy analyses will be carried out on the FAS.

8.3.2 Safety analysis sets (SAF)

SAF-OLP: For the open-label initial phase, the safety analysis set will include all patients as treated with at least one dose of IP in the open-label initial phase.

SAF-RTP: For the 28-day randomized treatment study phase, the safety analysis set will include all patients as treated with at least one dose of the 28-day randomized treatment study phase IP among those randomized.

All safety analyses will be based on the SAF sets.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

The primary efficacy endpoint in this study will be the model-based least squares means (LSMEANS) of all S-K values during the 28-day randomized treatment study phase Study Days 8-29.

8.4.2 Secondary efficacy variables

For the open-label initial phase, the secondary efficacy endpoints will include the following parameters:

- Exponential rate of change in S-K levels (blood)
- Mean change (absolute and percent (%) change) from baseline in S-K levels at all measured time intervals post dose (See Table 1)
- Proportion of patients who achieve normokalemia during the open-label initial phase at 24 hours and at the end of the open-label phase
- Time to normalization in S-K levels (normalization defined as S-K levels between 3.5-5.0 mmol/L, inclusive)

For the subsequent 28-day randomized treatment study phase, the secondary efficacy endpoints will include the following parameters:

- The proportion of patients who remain normokalemic (as defined by S-K levels between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during the 28-day randomized treatment study phase
- The number of days patients remain normokalemic during the 28-day randomized treatment study phase
- The mean change and mean percent change in S-K levels evaluated relative to both the open-label initial phase and the 28-day randomized treatment study phase baselines, respectively
- The time to hyperkalemia (defined as S-K ≥5.1 mmol/L)
- The mean changes in S-Aldo and P-Renin levels

8.4.3 Safety Variables

In this study, the following safety data will be collected: adverse events (AEs), vital signs, physical examinations, ECGs, clinical laboratory evaluations, and other electrolytes (specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

8.5 Methods for statistical analyses

All efficacy analyses will be performed separately for the open-label initial phase and the 28-day randomized treatment study phase using their respective full analysis sets. Safety data will be separately summarized in a descriptive manner on the safety analysis sets for the open-label initial phase and the 28-day randomized treatment study phase, respectively.

Analysis of data from the 28-day randomized treatment study phase will be performed after all patients have completed, discontinued or withdrawn from this phase. In addition, all relevant queries must be answered and the database must be locked and un-blinded for the 28-day randomized treatment study phase prior to the analyses.

Efficacy and safety data will be listed by patient. Descriptive statistics will include of the number of non-missing patients (n), mean, standard deviation, median, minimum, and maximum for continuous variables and counts and percentage for categorical variables. Where applicable, comparisons between each active dose treatment group vs. placebo control group will be performed using a 2-sample t-test.

Results of statistical analysis will be presented with a 95% confidence interval (CI) and two-sided p-value, unless otherwise stated.

Multiple testing strategy

An overall Type I error rate of 5% accounting for efficacy, in both phases of the study, will be maintained using a sequential closed testing procedure.

The analyses for the 28-day randomized treatment study phase will focus on randomized withdrawals. Treatment testing will proceed from high dose (ZS 10g) to low dose (ZS 5g) relative to placebo, with statistical significance (two-sided p-value ≤ 0.05) required for the high dose vs. placebo control in order to proceed to the low dose vs. placebo control.

Specifically, the following fixed hierarchical sequence will be employed; progression to the next test in the sequence will continue till a 2-sided p-value of > 0.05 is encountered, at which point further testing will cease. Explicitly, Table 6 will be implemented:

Table 6 Confirmatory Testing Sequence

Seq	Study Phase	Efficacy variable	Comparison
1	Initial[1]	open-label phase mean change from baseline of S-K 48 hours after first dose of ZS 10g	
2	Maintenance[2]	28-day randomized treatment study phase Days 8-29 mean S-K	ZS 10g qd vs. Placebo
3	Maintenance	28-day randomized treatment study phase Days 8-29 mean S-K	ZS 5g qd vs. Placebo
4	Maintenance	Proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomized treatment study phase at Study Days 29/Exit[3]	ZS 10g qd vs. Placebo
5	Maintenance	Proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) during the 28-day randomized treatment study phase at Study Days 29/Exit	ZS 5g qd vs. Placebo
6	Maintenance	Number of days patients remain normokalemic during the 28-day randomized treatment study phase	ZS 10g qd vs. Placebo
7	Maintenance	Number of days patients remain normokalemic during the 28-day randomized treatment study phase	ZS 5g qd vs. Placebo
8	Maintenance	Time to hyperkalemia (defined as S-K ≥ 5.1 mmol/L during the 28-day randomized treatment study phase)	ZS 10g qd vs. Placebo
9	Maintenance	Time to hyperkalemia (defined as S-K ≥ 5.1 mmol/L during the 28-day randomized treatment study phase)	ZS 5g qd vs. Placebo

1. Initial Study Phase refers to the Open-Label Initial Phase.
2. Maintenance Study Phase refers to the 28-day Randomized Treatment Study Phase.
3. Study Day 29/Exit refer to day of last dose of study treatment.

8.5.1 Analysis of the primary variable

The primary endpoint in this study will be the model-based LSMEANS of all available S-K values during the 28-day randomized treatment study phase Study Days 8-29. A log transformation will be applied to the S-K level, since historical data shows that S-K measurements follows a log-normal distribution, and also to stabilize the variance. A longitudinal model (SAS PROC MIXED) will then be used to simultaneously compare each active dose (high to low dose) versus placebo control for the 28-day randomized treatment study phase to estimate the least squares means Day 8-29 values. The model will include all S-K data collected at the schedule visits between Day 8-29 as response variables, and baseline for the open-label initial phase eGFR, open-label and double-blind randomized phase baseline S-K values as well as age (<55, 55-64, >64 years), country and baseline binary indicators for RAAS inhibitors, chronic kidney disease, heart failure, and diabetes mellitus as fixed effects terms and subject as the random effect term. In addition, the primary efficacy endpoint will be evaluated

in patients with hyperkalemia (defined as S-K ≥5.1 mmol/L) for the subgroups defined in Section 8.5.4. More details will be described in the SAP.

The S-K levels used for this analysis will be based on the Central Laboratory measurements. Missing Central Laboratory data for a given visit will be replaced by i-STAT values adjusted with the mean paired difference between i-STAT and S-K values collect at the same visit. More details on how to handle dropouts and missing data will be provided in the SAP.

8.5.2 Analysis of the secondary and additional variables

For the open-label initial phase, the mean and relative reduction in the secondary efficacy endpoints will be evaluated for all enrolled patients. The change from baseline will be assessed using a paired t-test, and a two-sided p-value ≤0.05 will be considered statistically significant.

The methods used to evaluate the secondary efficacy endpoints, for the 28-day randomized treatment study phase; to compare each active dose (high to low) vs. placebo control will be describe in the SAP.

Secondary efficacy endpoints will include:

- The proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of the 28-day randomized treatment study phase and during the 28-day randomized treatment study phase
- The number of days patients remain normokalemic during the 28-day randomized treatment study phase
- The mean change and mean percent change in S-K levels evaluated relative to both baselines
- The time to hyperkalemia (defined as S-K ≥5.1 mmol/L)
- The mean change in S-Aldo and P-Renin levels

In addition, the secondary efficacy endpoint at the end of the 28-day randomized treatment study phase will be evaluated in patients with hyperkalemia (defined as S-K ≥5.1 mmol/L) for the subgroups defined in Section 8.5.4. More details will be specified in the SAP.

Sensitivity analysis

Sensitivity analyses of the primary efficacy analysis and secondary efficacy analysis of the proportion of normokalemic patients at the end of and during the 28-day randomized treatment study phase will be performed to assess the robustness of the primary and these key secondary results. Details will be provided in the SAP.

8.5.3 Safety analysis

Separate safety analyses will be performed for the open-label initial phase and the 28-day randomized treatment study phase. Safety endpoints will include adverse events (AEs), serious AEs (SAEs), vital signs (VS), physical examinations, ECGs, clinical laboratory evaluations, and other electrolytes (specifically, serum calcium [S-Ca], serum magnesium [S-Mg], serum sodium [S-Na], serum phosphate [S-PO4], serum bicarbonate [S-HCO3], and blood urea nitrogen [BUN]).

Hypokalemia will be analyzed based on laboratory values and not by specific MedDRA terms.

The respective safety analysis will be undertaken on the safety analysis sets, separately for the open-label initial phase and for the 28-day randomized treatment study phase. Safety and tolerability data will be presented by treatment arm. Where appropriate, the safety analyses will include descriptive statistics, counts and percentages. More details will be described in the SAP. Only AE with date of onset during the respective observation period will be presented. Laboratory data and other investigations will be presented descriptively. More information will be provided in the SAP.

Adverse events will be classified according to Medical Dictionary for Regulatory Activities (MedDRA [latest version]). The type, timing (onset, duration), relationship, and severity of AEs will be reported. Withdrawal due to AEs will also be reported. Narratives will be written for every AE classified as serious or leading to withdrawal of IP. Safety results will be displayed separately for each of these phases.

8.5.4 Analysis in subsets of patients

The primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalemic (as defined by S-K between 3.5-5.0 mmol/L, inclusive) at the end of and during the 28-day randomized treatment study phase will be evaluated for the following subgroups:

- chronic kidney disease (CKD)
- diabetes mellitus (DM)
- heart failure (HF)
- those on RAAS inhibitors

More details will be described in the SAP.

8.5.5 Interim analysis

No interim analyses are planned.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of the AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).

The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the subjects or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to AstraZeneca and the head of study site.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last subject undergoing the study’.

The study is expected to start in Q1 2021 and to end by Q1 2022.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ZS.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Center staff or other party, according to the Data Management Plan.

Data will be entered into the WBDC system at the study site. Trained site staff will be entering the data as specified in the protocol and according to the eCRF instructions. Data entered into the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then undergo quality control and be validated as described in the Data Management Plan.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the World Health Organization Drug (WHODrug) Dictionary (version will be designated in the clinical study report). Classification coding will be performed by the Medical Coding Team at the AZ Data Management Center or other party.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The PI is responsible for signing the eCRF and this may be delegated to a trained Investigator.

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study is completed.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) external to AstraZeneca.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. Data Management will assure that the data collection tools for IVRS are tested and validated. External data reconciliation will be done with the clinical database as defined in the Data Management Plan.

10. REGULATORY, ETHICAL AND STUDY OVERSIGHT REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

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 authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed Informed Consent Form is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principle Investigator (PI) and AZ or AZ delegate.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the Clinical Study Protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any mew versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Data Quality Assurance

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

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

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.7 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

10.8 Source Data

- 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.

10.9 Study and Site Start and Closure

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

The first act of recruitment is the [first site to consent patients to the optional pre-screening ICF and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research 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.

11.LIST OF REFERENCES

Luo J et al 2016

Luo J, Brunelli SM, Jensen DE, et al. Association between serum potassium and outcomes in patients with reduced kidney function. Clin J Am Soc Nephrol 2016;11:90-100.

Packham DK et al 2015

Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 2015;372:222-31.

Kosiborod M et al 2014

Kosiborod M, Rasmussen HS, Lavin PT, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA 2014;312:2223-33

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

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

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

Appendix B Handling of Human Biological Samples

Chain of custody

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

The investigator at each site keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst 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 during for the remainder of the sample life cycle.

Withdrawal of Informed Consent for donated biological samples

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 analysed, 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[2] 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 documented and study site notified.

International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING 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 e.g., 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 e.g., 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 UN3373 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 C Guidance related to assessments and procedures during COVID-19 pandemic

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

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

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

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

   (a) Please accurately document all diagnoses, procedures, assessments, dosing interruptions, and sequelae in the eCRFs. All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP.

   (b) If a COVID-19 AE/SAE is reported, the investigator should determine whether the participant's investigational product should continue, be interrupted, or stopped in accordance with the CSP (section 3.9).

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

References:

https://www.fda.gov/media/136238/download

https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials

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