Statistical Analysis Plan

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A Phase II, Randomised, Double-Blind, Placebo Controlled, Parallel-Group, Multicentre, Three Month Duration Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy with Sodium Zirconium CyclosilicatE in Heart Failure (PRIORITIZE HF)

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Study Statistician

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Global Product Statistician

PPD

Date21/08/2020

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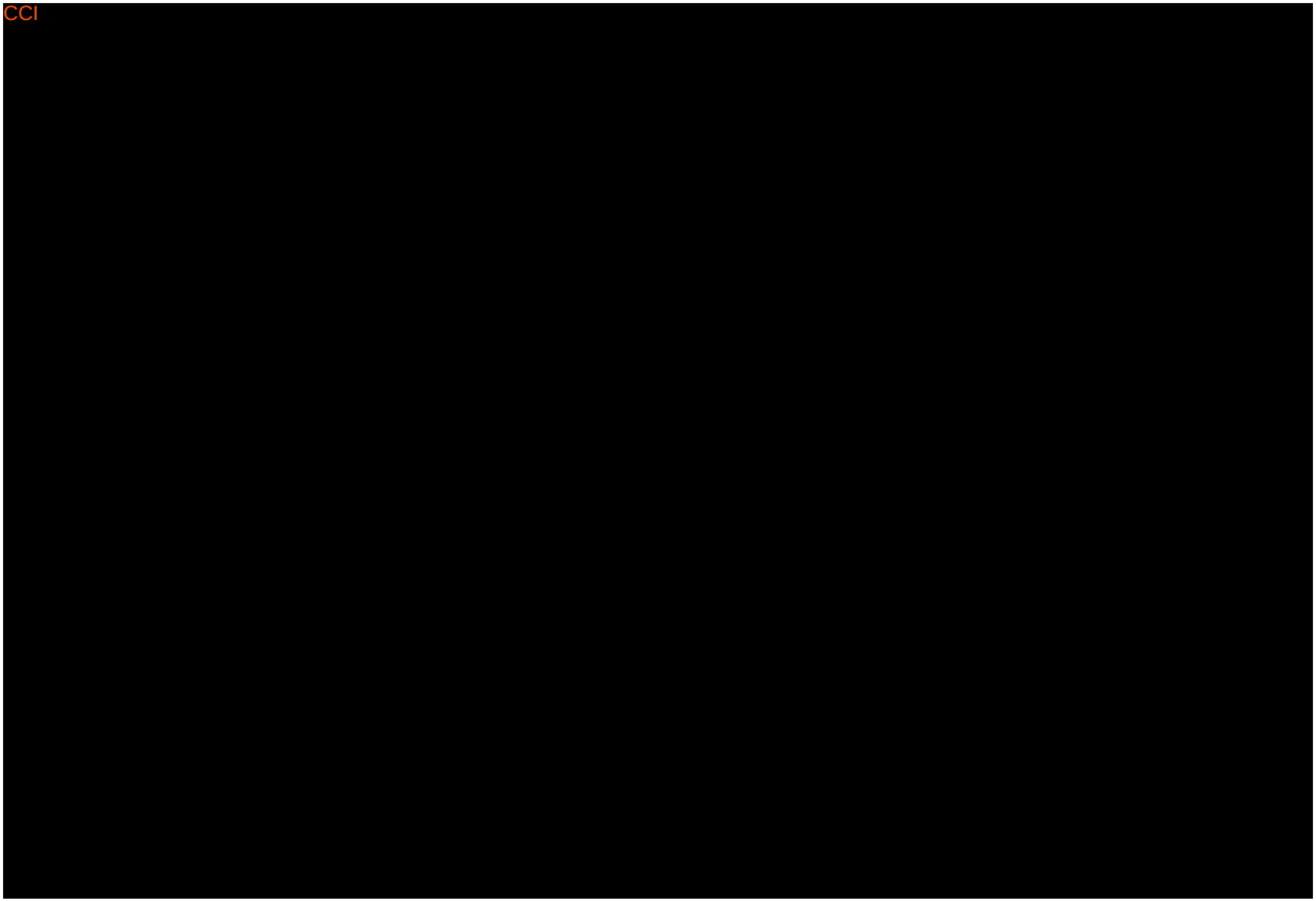
LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACEi	angiotensin converting enzyme inhibitors
AE	adverse event
ARB	angiotensin receptor blockers
ARNI	angiotensin receptor blocker and neprolysin inhibitors
ATC	anatomical therapeutic chemical
BP	blood pressure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSP	clinical study protocol
CSR	clinical study report
DAE	discontinuation of investigational product due to adverse event
DMC	Data Monitoring Committee
ECG	electrocardiograms
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
HF	heart failure
i-STAT-K	potassium measured using an i-STAT device
IP	investigational product
KCCQ	Kansas City cardiomyopathy questionnaire
MRA	mineralocorticoid receptor antagonist

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
NT-pro-BNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PGIC	Patient Global Impression of Change
qd	once a day
qod	every other day
RAAS	renin angiotensin aldosterone system
RAASi	renin angiotensin aldosterone system inhibitor
SAE	serious adverse event
SD	standard deviation
S-K	serum potassium
ZS	sodium zirconium cyclosilicate Note that sodium zirconium cyclosilicate can be abbreviated as either ZS or SZC in documents and refer to the same product.
tid	three times a day
UACR	urinary albumin to creatinine ratio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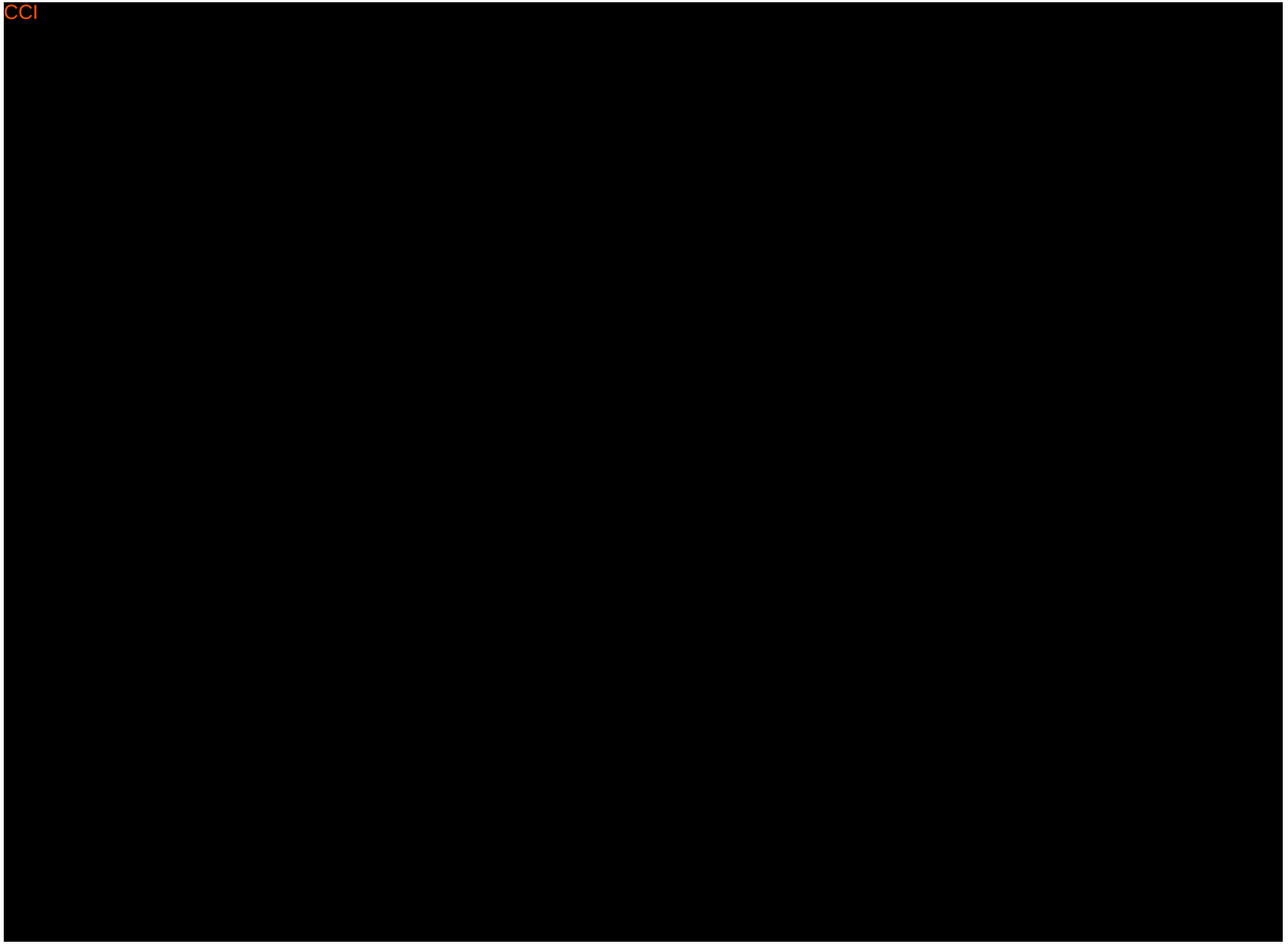
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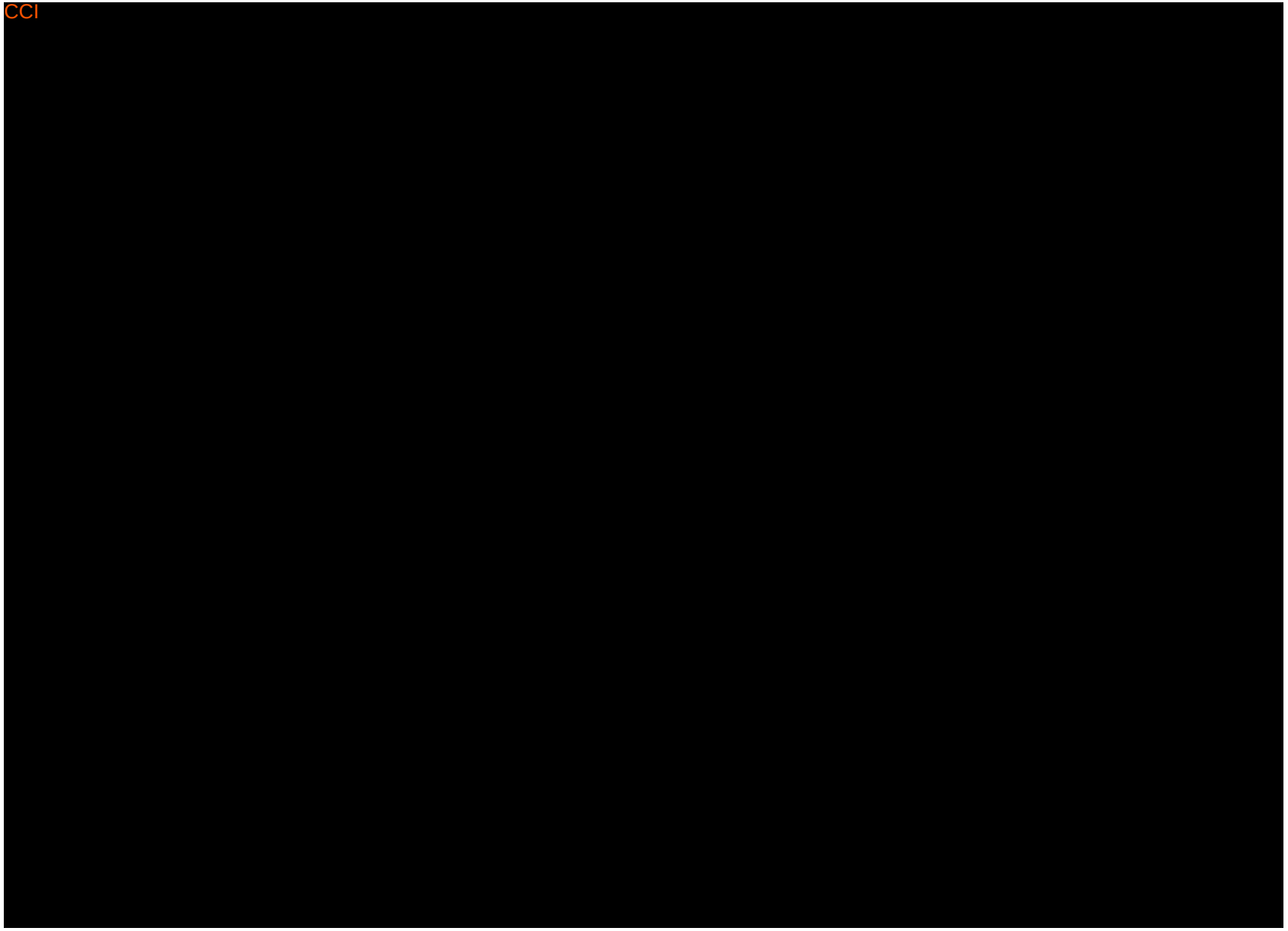
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1 STUDY DETAILS

1.1 Study objectives

Table 1 Study objectives

Primary Objective:	**Endpoint/Variable:**
To determine if there is a difference between SZC and placebo in RAAS blockade treatment.	Proportion of subjects in the following categories at 3 months: • No ACEi/ARB/ARNI or at less than target dose and no MRA • ACEi/ARB/ARNI at target dose and no MRA • MRA at less than target dose • MRA at target dose
Safety Objective:	**Endpoint/Variable:**
To evaluate the safety and tolerability of SZC in this patient population.	• Serious Adverse Events (SAEs) • Discontinuation of IP due to Adverse Events (DAEs) • Adverse Events (AEs) • Changes in clinical laboratory parameters, including assessment of creatinine and renal function (eGFR). • Vital signs • ECG
To explore whether SZC compared with placebo will affect the incidence of high and/or low S-K levels.	Number of subjects and number of events with central lab levels of S-K: • >6.0 mmol/L • >5.5 mmol/L • <3.5 mmol/L • <3.0 mmol/L

Exploratory Objectives	**Endpoint/Variable:**
To explore the difference between SZC and placebo in RAAS blockade treatment in subjects with local lab-K[a] > 5.0 mmol/L at last assessment before randomization.	Proportion of subjects in the following categories at 3 months: • No ACEi/ARB/ARNI or at less than target dose and no MRA • ACEi/ARB/ARNI at target dose and no MRA • MRA at less than target dose • MRA at target dose
To explore the difference between SZC and placebo in RAAS blockade treatment in subjects with local lab K ≤ 5.0 mmol/L at last assessment before randomization.	Proportion of subjects in the following categories at 3 months: • No ACEi/ARB/ARNI or at less than target dose and no MRA • ACEi/ARB/ARNI at target dose and no MRA • MRA at less than target dose • MRA at target dose
To explore the difference between SZC and placebo in facilitating the initiation and maintenance of MRA treatment	• Proportion of subjects treated with MRA at 3 months • Proportion of subjects at target dose of MRA therapy at 3 months
To explore the difference between SZC and placebo in Renin angiotensin aldosterone system inhibitor (RAASi) therapy	Proportions of subjects on higher dose of RAASi compared to baseline • Mean equipotent doses of MRA at 3 months • Dose intensity score as calculated in Vasudevan et al (Vasudevan et al 2017), with the exception of only considering RAASi drugs • A scoring system to assess the intensity of RAASi therapy (see Section 3.3 for details)

To explore change of blood pressure (BP) in the SZC group compared with the placebo group.	Change in systolic and diastolic BP from baseline.
To explore change of urinary albumin to creatinine ratio (UACR) in the SZC group compared with the placebo group.	Change in UACR from prior to the first increase in RAASi therapy (Visit 3), in the subset of subjects with albuminuria (UACR > 30 mg/g) at Visit 3.
To explore change in NYHA class in the SZC group compared with the placebo group.	Change in NYHA class from baseline.
To explore the effect of treatment with SZC versus placebo on the Patient Global Impression of Change (PGIC) and Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score.	• Change in health status measured by PGIC. • Change from baseline measured at 3 months in the overall summary score of KCCQ, a specific HF patient reported outcome questionnaire.
To explore any change in biomarkers as surrogates for cardiac and renal function associated with SZC.	Changes in biomarkers NT-pro-BNP, and troponin.
To collect and store samples of plasma and serum for future exploratory biomarker and (optional) genetic research.	Results to be reported outside of the clinical study report (CSR).

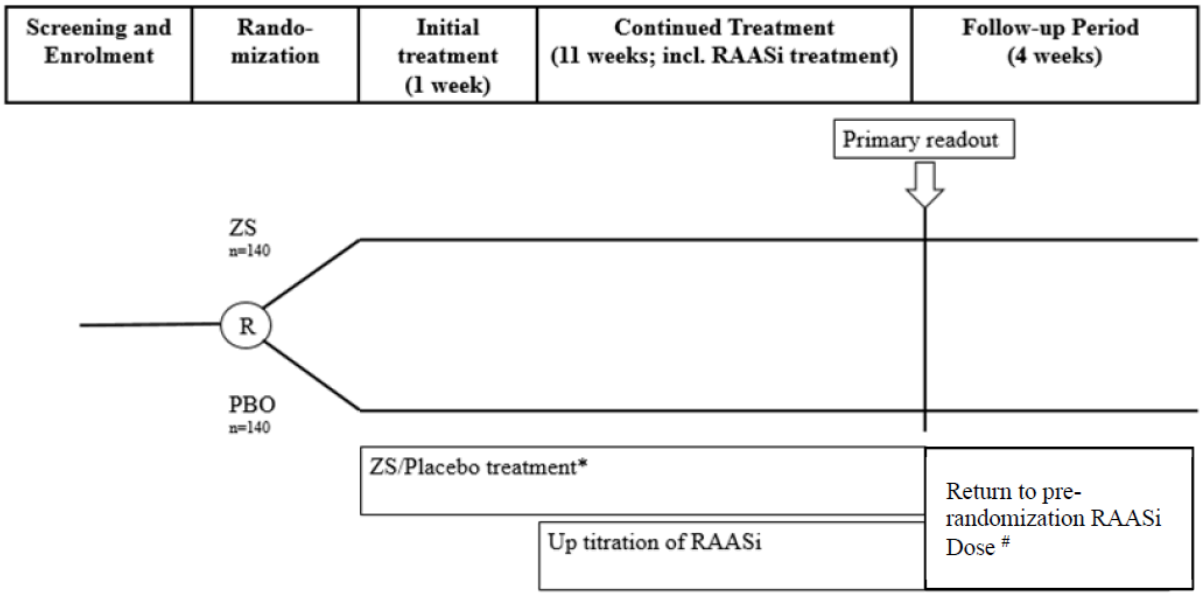
[a] i-STAT for patients enrolled under CSP version 3 or earlier.

1.2 Study design

This is an international, multicentre, parallel group, randomised, double-blind, placebo-controlled Phase II study to evaluate the benefits and risks of using sodium zirconium cyclosilicate (SZC) to intensify RAASi therapy. Patients with chronic heart failure (NYHA II-IV) and mild hyperkalaemia, or at high risk of developing hyperkalaemia, will be enrolled. Eligible subjects will be randomised in a 1:1 ratio to receive SZC or placebo for 3 months while titrating RAASi therapies.

The general study design is summarised in Figure 1. Note that, as per CSP version 3 and earlier, i-STAT, and not local lab, was used to evaluate baseline K.

Figure 1 Study design



* Subjects with local lab-K > 5.0 mmol/L will receive SZC 10g tid or placebo for 48h before starting continued treatment with SZC 5g qd or placebo; Subjects with local lab ≤ 5.0 mmol/L will immediately start continued treatment with SZC 5g or Placebo (PBO) qd. Continued treatment will be titrated within the range 5g qod to 15g qd.

After the end of randomised therapy (Visit 8 or early treatment discontinuation), the investigator should return to the original RAASi dose the patient was on prior to randomization and will manage the subject as per standard of care. In instances in which the investigator had down-titrated or stopped RAASi medications, then the subject should remain on the lowest dose at the end of randomized therapy.

1.3 Number of subjects

The study will employ a 1:1 randomization scheme. A sample size of 280 subjects will allow for estimation of the effect in the primary objective. Due to lack of prior knowledge of the distribution of the primary endpoint categories in the placebo group, the following considerations were made with regards to sample size. Assuming a difference in proportion of MRA use at 3 months of 0.2 between treatment groups, a sample size of 140 subjects per group provides at least 90% power for a significance level of 5% using a chi-square test.

Due to the COVID-19 pandemic the study was prematurely terminated with a total sample size of 182 patients.

2 ANALYSIS SETS

2.1 Definition of analysis sets

For purposes of analysis, the following analysis sets are defined:

Analysis set	Description
Enrolled	All subjects who sign the informed consent form.
Full analysis set	All randomised subjects.
Safety analysis set	All subjects randomly assigned to study treatment and who take at least 1 dose of investigational medicinal product.

The Full analysis set will be used in the analysis of the primary objective.

2.2 Violations and deviations

The important protocol deviations will not imply exclusion from any analysis and will be summarized by randomized treatment group. A list of possible important protocol deviations can be found in section 4.1 in the Non-Compliance Handling Plan.

In addition, COVID-19 related important and non-important protocol deviations will be summarized and listed.

3 VARIABLES

Whenever an assessment or measurement at 3 months is referred to, it is the assessment/measurement at visit 8 that will be used, provided this visit took place at least 77 days after the patient was randomized into the study. Note that, during the study interruption, and in case of early study discontinuation due to COVID-19, patients were called to attend visit 8 prematurely. In summary tables, visit 8 measurements occurring 3 months post randomization, as per original study schedule, are summarized separately.

If visit 8 occurred earlier than 77 days post-randomization, the 3 months measurement is regarded as missing (and, for the primary analysis, is imputed).

In the case of the subject who at the same time takes more than one medicine within ACEi/ARB/ARNI class or within MRA class, the medicine with the largest equipotent dose (see the definition of equipotent dose in section 3.3) will be selected per RAASi class (ACEi/ARB/ARNI and MRA separately) for all derivations and analyses in which RAASi dose is directly used.

3.1 Primary variable

The primary outcome measure is the classification of subjects in the following four categories at 3 months:

- No ACEi/ARB/ARNI or at less than target dose and no MRA
- ACEi/ARB/ARNI at target dose and no MRA

- MRA at less than target dose
- MRA at target dose.

The RAASi dose used in the primary variable will be the dose the subject is on before any potential RAASi titration/change on the day of visit 8, i.e. the RAASi treatment(s) will have to have a start date before the date of visit 8 and either be ongoing at visit 8 or have the visit 8 date as stop date.

For the purpose of the primary analysis, missing RAASi dose data at 3 months will be imputed by Multiple Imputation technique implemented in SAS® in PROC MI. A detailed description of the imputation algorithm can be found in Section 4.2.1.

Wherever a range is provided in the target dose column in Table 5 in the Clinical Study Protocol (CSP), the lower end of the range will be considered the target dose in the derivation of the primary variable. If a dose reported in the electronic case report form (eCRF) is equal to or higher than the defined target dose, the reported dose will be assumed to be the target dose in the categorization.

3.1.1 Variables for sensitivity analyses

The primary variable and outcome measure will also be derived based on non-imputed data, i.e. using only available data at 3 months.

In addition, if the primary variable is missing at 3 months, the worse (lower) of the doses at the last two scheduled visits, randomization visit and onwards, with available data (for ACEi/ARB/ARNI and MRA respectively) will be used to derive the primary variable. If the subject doesn't have two available non-missing values, then the dose(s) will be assumed to be zero.

A sensitivity analysis aiming at evaluating the impact of COVID-19 on the data will also be performed.

3.2 Secondary variables

Not Applicable.

3.3 Exploratory variables

Subject treated with MRA at 3 months

The binary variable "subject treated with MRA at 3 months (yes/no)" will be defined as yes if the subject is on an MRA dose greater than 0 at 3 months, and defined as no if subject is on no MRA dose at 3 months, or left as missing if 3-months data is missing.

Subject at target dose of MRA at 3 months

The binary variable "subject at target dose of MRA at 3 months (yes/no)" will be defined as yes if the subject is on an MRA dose equal to or greater than the target dose as specified in CSP Table 5 at 3 months, and defined as no if subject is on an MRA dose less than the target dose or on no MRA at 3 months, or left as missing if 3-month data is missing.

Equipotent dose of MRA ≥ 50% at 3 months

The binary variable "Equipotent dose of MRA > 50% at 3 months (yes/no)" will be defined as yes if the subject is treated with equipotent MRA dose greater than 50% at 3 months and defined as no if the subject is on an equipotent MRA dose equal to or less than 50% at 3 months, or left as missing if 3-month data is missing.

Higher dose of RAASi compared to baseline

The values of the binary variable "higher dose of RAASi compared to baseline (yes/no)" will be derived for multiple time points as specified in Section 4.4 . ACEi/ARB/ARNI and MRA medications will be considered separately. The equipotent dose defined below (in 'Equipotent doses of MRA') will be compared.

If the dose of either ACEi/ARB/ARNI or MRA drug has been increased at a visit as compared to baseline, then the binary variables "higher dose of RAASi compared to baseline" will be set to 'yes', otherwise will be set to 'no'.

Equipotent doses of RAASi

In general, equipotent dose of a RAASi treatment at a particular time point is defined as the ratio of achieved dose at that occasion and the corresponding target dose provided in Table 5 in the CSP. When the frequency of drug intake is different than qd, then total daily dose is used for calculations. In particular, Sacubitril + Valsartan is administrated as 24/26 mg bid, 49/51 mg bid, or 97/103 mg bid, where the latter is the target dose. Corresponding equipotent doses are 25%, 50% and 100%.

The values of equipotent doses (denoted below as X) of ACEi/ARB/ARNI or MRA will be converted into categories, to be further used for the primary endpoint construction, as follows:

- $X \leq 0\%$ – consider as "no dose" category
- $0 < X < 100\%$ – consider as "some, but less than target dose" category
- $X \geq 100\%$ – consider as "target dose" category.

Dose intensity score

A "RAASi dose intensity score" based on the drug/dose intensity scores presented in Vasudevan et al (Vasudevan et al 2017) will be derived based on RAASi treatment data from visit 2, 5, 7 and 8 respectively (i.e. baseline and approximately at 1, 2 and 3 months) using the following rule, where target dose is the target dose in CSP Table 5 (lower limit if a range is given):

- Score value 0: if patient receives no dose
- Score value 1: if 0 < dose < (target dose)/2
- Score value 2: if (target dose)/2 to ≤ dose < target dose
- Score value 3: if dose ≥ target dose.

A score will be derived for a subject with respect to ACEi/ARB/ARNI and MRA separately.

RAASi therapy intensity

Categorize the dose of ACEi/ARB/ARNI and MRA, respectively, as is done for the primary endpoint, namely into

- no dose
- some, but less than target dose
- target dose.

There are nine possible combinations of such ACEi/ARB/ARNI and MRA dose categories for a subject. In an attempt to rank the intensity of RAASi therapy, an order of probable clinical benefit for the combined dose categories was defined by the members of the Executive Committee as follows:

	Subject dose category	
Ascending order of category of RAASi therapy intensity	**ACEi/ARB/ARNI**	**MRA**
0	No dose	No dose
1	Some	No dose
2	No dose	Some
3	Target	No dose
4	Some	Some
5	No dose	Target
6	Target	Some
7	Some	Target
8	Target	Target

Change from baseline in BP

Change from baseline in systolic and diastolic BP will be derived as part of the standard vital signs evaluation (see Section 3.4.4).

Change in UACR

As per the CSP, urinary albumin and creatinine will be provided by the central laboratory for Visit 3 and Visit 8 only. Urinary albumin to creatinine ratio (UACR) will be calculated as the ratio of urine albumin and urine creatinine. The change in UACR is defined as the difference between the Visit 8 and Visit 3 values, respectively.

NYHA

The NYHA classification values are provided in Appendix G in the CSP and will be used directly in the analysis.

PGIC and KCCQ questionnaires

PGIC and KCCQ questionnaires are provided in Appendix H in the CSP.

PGIC values will be used directly in the analysis.

The KCCQ is a self-administered disease specific instrument and has shown to be a valid, reliable and responsive measure for patients with HF (Green et al 2000, Spertus et al 2005). The KCCQ consists of 23 items measuring HF-related symptoms, physical limitations, social limitations, self-efficacy, and health-related quality of life.

The Overall Summary Score incorporates the symptom and physical limitations, quality of life and social limitations domains into a single score. Higher scores represent a better outcome. For more details regarding the Overall Summary Score derivation, see KCCQ-Scoring-Instructions document.

The Total Symptom Score incorporates the frequency and limitations of the symptoms into a single score. Higher score represents a better outcome. For more details regarding the Total Symptom Score derivation, see KCCQ-Scoring Instructions document

The Clinical Summary Score incorporates the Total Symptom Score and the Physical Limitation Score into a single score. Higher scores represent a better outcome. For more details regarding the Clinical Summary Score derivation, see KCCQ-Scoring-Instructions document.

3.4 Safety variables

3.4.1 Adverse events

Adverse Events will be collected from time of signature of informed consent form throughout the treatment period and including the follow-up period until the last contact in the study.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 21.0 or higher.

3.4.2 Laboratory safety variables

The baseline value is defined as the last observation prior to first IP dose.

Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI equation (Levey at al 2009) for each time-point where creatinine is measured, using central laboratory creatinine.

Urinary albumin and creatinine will be provided by the central laboratory and will be used to calculate urinary albumin to creatinine ratio (UACR).

3.4.3 Physical examinations

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. Hence, the results from the post-baseline physical examinations will be part of the AE reporting and not presented separately.

3.4.4 Vital signs

Vital signs assessments will consist of weight, pulse and systolic and diastolic BP measurements. Changes from baseline will be derived. The baseline value is defined as the last observation prior to the first IP dose.

3.4.5 ECGs

12-lead electrocardiograms (ECG), with PR, QRS and QT intervals automatically calculated, will be obtained at screening, visit 8/end-of-treatment visit and visit 10.

QTc will be derived. Frederica's correction will be used, with QTcF obtained from existing measurements as $QTcF = QT/(60/HR)^{1/3}$.

The ECG baseline value will in general be the value obtained at the screening visit, since ECG is not measured at the randomization visit according to the study plan. If multiple baseline assessments exist, the baseline value will be the last observation prior to IP dose.

3.4.6 S-K

For the tabulation of high and low S-K levels, central laboratory S-K will be used.

3.4.7 Other

Exposure to study drug will be defined as total length of period on study drug, calculated for each subject as date of last dose - date of first dose +1.

Actual exposure to the study drug will be defined as the number of days a subject was on IP, excluding any dose interruptions.

The percentage of study drug compliance for the randomized treatment period will be derived for each subject based on sachet counts, converted into grams of study drug, as the number of sachets taken (dispensed – returned) multiplied by 5 (as each sachet contains 5 mg of drug), relative to the expected grams of study drug taken. The expected amount of dose taken will be based upon the planned administration of study drug (dose and frequency) recorded by the investigator.

4 ANALYSIS METHODS

4.1 General principles

The primary and explorative analyses will be based on the Full analysis set including all randomised subjects. Subjects will be analysed according to their randomized study medication.

In safety analyses the Safety analysis set will be used. Erroneously treated subjects (e.g. those randomized to SZC but actually given placebo throughout the study or vice versa) will be accounted for in the actual treatment group. A subject who in error has received both SZC and placebo will be accounted for in the randomized treatment group.

No imputation will be done for missing or partial missing dates, except for start and end date for concomitant medication, which will be imputed as follows:

- Missing start day - impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing start day and month – impute 1st January unless year is the same as first dose date, then impute first dose date. Ensure that the start date is prior to the end date of the concomitant medication.
- Start day completely missing - impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date of the concomitant medication.

When imputing a start date ensure that the new imputed date is sensible, i.e. is prior to the end date of the medication.

- Missing end day - impute the last day of the month unless month is same as month of first dose of study drug then impute last dose date.
- Missing end day and month – impute 31st December unless year is the same as first dose date then impute last dose date.
- End date completely missing - if the ongoing flag is missing, then assume that the medication is still being taken, i.e. do not impute a date. If the medication has stopped and start date is prior to first dose date, then impute the 1st dose date. If it started on or after first dose date, then impute to be the last dose date.

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

Analyses will be performed by AstraZeneca or its representatives.

Data will be presented following the AZ Corporate CSR/HLD Reporting Standards.

4.2 Analysis methods

4.2.1 Analysis of the primary variable

The primary objective is to determine if there is a difference between SZC and placebo in RAASi treatment. The null hypothesis is that there is no difference between treatments in the distribution of proportion of subjects in the RAASi treatment categories, and the alternative hypothesis is that there is a difference. The hypothesis will be tested at a significance level of 5%.

As already indicated in Section 3.1, missing RAASi dose data at 3 months requires special attention before conducting the primary analysis. Toward this aim, Multiple Imputation technique will be used. It is assumed that the missing data mechanism operating in this setting is Missing At Random and data for subjects with missing values will be imputed based on observed data from subjects within their own treatment arm.

The general workflow of the primary analysis will be outlined. The first step in the proposed procedure is to impute missing data for the primary variable with PROC MI implemented in SAS®, resulting in M complete datasets. Then, the hypothesis of a treatment difference (SZC vs placebo) in the distribution of RAASi treatment across the four categories of the primary outcome measure will be tested using a chi-square test for homogeneity, applied for each of M complete datasets. Lastly, M chi-square test statistics will be combined into a single value, allowing the computation of a final p-value of the procedure.

The primary outcome measure is derived based on doses of the two classes of RAASi treatments, i.e. ACEi/ARB/ARNI and MRA. These are converted to one of four categories as specified in the definition of the primary variable, and the categories will be imputed for subjects with missing data at 3 months. Since it is allowed for subjects to switch between different RAASi medicines throughout the study, the RAASi categories (see definition, Section 3.3) will be used as categorical response variables in the imputation method.

Monotone methods in PROC MI will be utilized. A monotone method creates multiple imputations by imputing missing values sequentially over the variables taken one at a time, according to a specified order of variables to impute. In particular, a monotone discriminant function method will be used to impute the RAASi categories. The model will include RAASi category at 3 months as the outcome variable and the following covariates: RAASi category, local lab-K, eGRF and systolic blood pressure measured at the last visit before the 3 months visit when all the covariates' data are available. The rationale to use such covariates in the imputation models is that the decision regarding the titration of RAASi treatments is taken based on, among others, local lab-K, eGFR, blood pressure levels and may depend indirectly on the previous RAASi dose.

Imputation will not be performed for subjects with no available post baseline values of equipotent doses of ACEi/ARB/ARNI or MRA.

In the multiple imputation process, ≥100 iterations will be performed. In order to allow to reproduce the results of multiple imputation procedure, seed to begin random number generator will be specified as 8823.

In next step, the primary outcome measure will be tested using a chi-square test for homogeneity for each complete dataset.

Finally, M results of the chi-square test will be combined according to the following formulas:

$$D_x = \frac{\frac{\overline{\chi^2}}{k} - \frac{M+1}{M-1}\bar{r_x}}{1+\bar{r_x}}$$

where $\overline{\chi^2} = \frac{1}{M}\sum_{m=1}^{M}\chi_m^2$; $\bar{r_x} = \left(1+\frac{1}{M}\right)\frac{1}{M-1}\sum_{m=1}^{M}\left(\sqrt{\chi_m^2} - \frac{1}{M}\sum_{m=1}^{M}\sqrt{\chi_m^2}\right)^2$

and k is the number of degrees of freedom in the single chi-square test.

The pooled p-value can be obtained from F distribution with k and v_x numerator and denominator, respectively, degrees of freedom as follows:

$$\text{p-value}=\Pr(F_{k,v_x} > D_x)$$

where $v_x = k^{-\frac{3}{M}}(M-1)(1+\frac{1}{\bar{r}_x})^2$.

The pooled p-value will be compared to 5 % significance level.

For more details regarding the pooling procedure, see Ratitch et al 2013 or Li et al 1991.

The resulting pooled p-value will be presented alongside the averaged proportion of subjects in the four categories over M multiple imputation datasets. The denominator for the proportions will be the number of Full analysis set subjects with a non-missing value for the RAASi category (after imputation) in the respective treatment group.

4.2.2 Sensitivity analyses

Sensitivity analyses of the primary analysis will be performed

(i) by using only available non-imputed RAASi dose data at 3 months

(ii) by using the worse of the last two dose observations carried forward (see Section 3.1.1 for full derivation of this variable).

(iii) by removing the observations potentially affected by COVID-19, defined as observations obtained on visits with visit dates later than 2020-03-11, and repeating the primary analysis on the resulting data set.

For sensitivity analysis (i) and (ii), the resulting chi-square p-value will be presented alongside the number and proportion of subjects in the four categories of the primary outcome measure. The presentation for the (iii) will be the same as that for the primary endpoint.

4.3 Analysis of secondary variables

Not Applicable.

4.4 Analysis of exploratory variables

Exploratory objectives will be presented using summary statistics, and where specified below an estimated treatment difference with 95% CI will also be presented. No formal statistical inference is planned for exploratory endpoints, therefore no correction for multiplicity will be applied. For this reason, confidence intervals provided for any of the exploratory variables should be interpreted with great caution.

Except for sub-group analyses of the primary endpoint, exploratory variables will be based on available data at the visits in question.

Subgroups for explorative subgroup analyses applied to the primary outcome measure will be defined as follows:

1. Subjects with K >5.0 mmol/L at last assessment before randomization vs subjects with K ≤5.0 mmol/L at last assessment before randomization.

2. Subjects randomized pre CSP amendment 4, defined as randomization date less of equal to 12th June 2019 vs subjects randomized post CSP amendment 4.

Baseline K subgroups are determined by the latest non-central lab potassium assessment before randomization. This could be either an i-STAT or a local lab assessment, mainly depending on the version of the CSP (version 4 or earlier) under which patients were enrolled in the study.

Subject treated with MRA at 3 months

Frequency and percentage of subjects treated with MRA at 3 months will be calculated per treatment group. In addition, the difference in proportions between the two treatment groups and a 95% CI of the difference, based on standard normal distribution approximation, will be calculated.

Subject at target dose of MRA at 3 months

Frequency and percentage of subjects at target dose of MRA at 3 months will be calculated per treatment group. In addition, the difference in proportions between the two treatment groups and a 95% CI of the difference, based on standard normal distribution approximation, will be calculated.

Subject at the equipotent dose of MRA ≥ 50% at 3 months

Frequency and percentage of subjects treated with MRA > 50% (equipotent dose) will be calculated per treatment group. In addition, the difference in proportions between the two treatment groups and a 95% CI of the difference, based on standard normal approximation, will be calculated.

Higher dose of RAASi compared to baseline

Frequency and proportions will be presented by treatment group for every scheduled post-baseline time point through Visit 3 and Visit 8. In addition, the difference in the proportions between the treatment groups and its 95% confidence intervals, based on standard normal distribution approximation, will be provided.

Equipotent doses of MRA at 3 months

Analysis of the endpoint will consist of presenting the frequency and percentage of subjects with particular equipotent doses encountered in the study (expressed in %) falling into the

categories/intervals that include “0%”, “25%”, “50%”, “75%”, “100%”, “>100%”, “Other”, displayed per treatment group.

In addition, mean MRA equipotent dose per treatment group will be presented, along with the difference in the means of SZC and placebo arms, and 95% confidence interval for the difference based on standard normal distribution approximation.

Dose intensity score

The “RAASi dose intensity score” based on Vasudevan et al (Vasudevan et al 2017) will be presented per treatment group as ordered categorical data with frequency and percentage of subjects in the three score categories per time point (visit 2, 5, 7 and 8).

RAASi therapy intensity at 3 months

Frequency and proportion of subjects in the RAASi therapy intensity categories at 3 months will be presented by treatment group.

Change from baseline in BP

Change from baseline in systolic and diastolic BP will be presented per treatment group using descriptive statistics as part of the standard safety presentations (see Section 4.5.3).

Change in UACR at 3 months

The analysis of change in UACR from Visit 3 to Visit 8 will be performed in the subset of subjects with albuminuria (UACR > 30 mg/g) at Visit 3 and displayed using standard summary statistics (n, mean, SD, median, quartiles, minimum and maximum) per treatment group. In addition, the difference in the means of SZC and placebo arms, and 95% confidence interval for the difference, based on standard normal distribution approximation, will be reported. The analysis will be replicated using UACR values converted to standard units.

NYHA at 3 months

NYHA classification will be summarized with shift table presenting changes from baseline to the 3 months measurement. Furthermore, the proportion of subjects with no worsening of NYHA classification at Visit 8 compared to baseline will be analyzed by a logistic regression model with treatment group and baseline NYHA as covariates. The odds ratio between treatment groups and its 95% confidence interval will be reported.

PGIC and KCCQ questionnaires at 3 months

For PGIC, frequency and percentage of subjects selecting each answer at 3 months will be shown per treatment group.

Summary statistics (n, mean, SD, median, quartiles, minimum and maximum) per treatment group will be provided for the change in KCCQ Overall Summary Score, Total Symptom Score and Clinical Summary Score at 3 months as compared to baseline, as well as the difference in the means of SZC and placebo arms, and 95% confidence interval for the difference based on standard normal distribution approximation.

Biomarkers

NT-pro-BNP and troponin data will be provided by the central laboratory and as such, will be summarized per treatment group with a standard laboratory table presenting n, mean, SD, median, quartiles, minimum and maximum at baseline and change from baseline at Visit 3, 8 and 10, if available.

Increase in RAASi

The eCRF captures the primary reason for not increasing RAASi dose at each visit. This data will be tabulated descriptively per treatment group.

The number of subjects with RAASi increase at each visit will also be tabulated.

Other

Number and percentage of subjects with S-K measurements in the interval [3.5, 5.0] mmol/L will be presented per treatment group and visit (only scheduled visits).

S-K will also be summarized per treatment group with descriptive statistics of observed and change from baseline values (n, mean, SD, median, quartiles, minimum and maximum) over time (only scheduled visits). In addition, a graph showing mean S-K values over time (only scheduled visits) with SD per treatment group will be presented.

4.5 Analysis of safety variables

Whenever “during treatment” is used in tabulations of safety data, the treatment period is considered to continue up to (and including) the date of last dose of study drug plus 1 day.

4.5.1 Adverse events

Summaries of adverse events will primarily include all events with a start date on or after the first dose. However, some of the tables (an overall summary of AEs and a summary by SOC and PT) will also be replicated for “during treatment” time period.

Adverse events for non-randomized subjects will be presented separately, in the form of a listing.

Number and percentage of subjects with events will be tabulated per treatment group by preferred term and system organ class. Adverse events will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Serious AEs, AEs leading to discontinuation of IP will be summarized in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to IP discontinuation will be summarized for each treatment group as applicable.

Number and percentage of subjects with fluid overload/oedema related events will in addition be presented separately. Fluid overload/oedema related events will be defined by the following MedDRA terms: Fluid overload, Fluid retention, Generalised oedema, Hypervolaemia, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling.

4.5.2 Laboratory safety variables

All summaries of clinical chemistry/haematology variables collected for the purpose of safety evaluation will be based on samples analyzed at the central laboratory, and presented in SI units.

Laboratory data, including eGFR, will be summarized by presenting shift tables using normal ranges (baseline to most extreme value during treatment), and by presenting summary statistics of observed and change from baseline values (n, mean, SD, median, quartiles, minimum and maximum). Changes outside pre-specified criteria will be listed and summarized. For eGFR, the shift table will be based on the intervals <15, 15 to <30, 30 to <45, 45 to <60, 60 to <90 and ≥90 ml/min/1.73m^2.

The incidence of clinically notable lab abnormalities will be summarized by presenting data on subjects with potential Hy's law.

4.5.3 Vital signs

Vital sign data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarized by presenting a shift table of vital sign measurements classified by the investigator as clinically significant or not, baseline to minimum and maximum values during treatment. Measurements not marked as clinically significant will be assumed to be judged normal, while clinically significant are judged to be abnormal.

4.5.4 ECGs

ECG intervals (PR, QRS, QT and QTc) will be summarized by presenting summary statistics of observed and change from baseline values. Fridericia's correction will be used for QTc. The incidence of clinically notable ECG abnormalities will be summarized. QTc values falling outside pre-defined criteria will be tabulated, during treatment and during study.

4.5.5 S-K

Number and percentage of subjects with central lab S-K < 3.5 mmol/L, <3.0 mmol/L and < <2.5 mmol/, as well as those with > 5.0 mmol/L , >5.5 mmol/L >6.0 mmol/L and >6.5 mmol/L during the study (i.e. treatment period and follow-up) will be presented per treatment group. The denominator will be the total number of subjects in the Safety analysis set per treatment group.

All available samples, including unscheduled samples, will be included in above calculations.

4.5.6 Other

Duration of exposure (days) will be presented descriptively, and exposure over time will be presented in a figure. Actual exposure, by dose, will be tabulated. Summaries of dosing pattern (average daily dose, number and frequency of dose titrations) during the study will also be presented.

Both exposure and actual exposure will be listed.

4.6 Analysis of demographics and baseline characteristics

Demographics and subject characteristics, relevant medical history, medications at the time of randomization and subject disposition will be summarized by treatment group using frequency and percentages (for categorical variables) and descriptive statistics of n, mean, standard deviation, minimum, median, and maximum (for continuous variables) using the Full analysis set.

4.7 Analysis of concomitant and baseline medication

Baseline medication is defined as medication with at least one dose taken before date of randomization and with no stop date before date of randomization.

Concomitant medications are defined as medications taken post randomization, including the randomization day.

The frequency of baseline and concomitant medication, including RAASi medications, will be presented per ATC class and treatment group using the Full analysis set. Separate tables will be created for RAASi and non-RAASi medications.

Summaries of restricted concomitant medications that were started or ongoing after randomization will also be presented. Restricted medications will be identified in eCRF data based on ATC codes (and drug code, if needed). Restricted concomitant medications include the medications listed in Table 2.

Subject receiving restricted concomitant medications will not be excluded from any statistical analyses.

4.8 Other

Study drug compliance (%) will be presented descriptively, including mean, standard deviation (SD), median, quartiles and 5% and 95% percentiles.

4.9 COVID-19 related analyses

To assess the degree of missingness for the study, number of patients attending the different study visits, as well as number of patients still on treatment, will be tabulated, for visits occurring after the start of the pandemic, defined as the 11th of March 2020. Visit type for such visits will be tabulated and listed. COVID-19 related protocol deviations (both important and non-important) will be tabulated and listed. In addition, a summary table illustrating the study disruptions that could be attributable to COVID-19, where e.g. the number of subjects in the study at the start of the pandemic is displayed, per treatment group, will be provided.

5 INTERIM ANALYSES

Not applicable.

5.1 Data Monitoring Committee (DMC)

An independent data monitoring committee (also called a Safety Review Committee) will be utilized for this study. The responsibilities of the Safety Review Committee will be specified in a Safety Review Committee charter.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

7 REFERENCES

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8 APPENDIX

8.1 Restricted concomitant medications

Table 2 Restricted concomitant medications

Class of drug	Drugs	ATC codes
Potassium binders	Polystyrene sulphonate, patiromer, zirconium cyclosilicate	V03AE01 V03AE09 V03AE10
Potassium supplements		A12BA

8.2 KCCQ scoring instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

   - Code responses to each of Questions 1a-f as follows:

     Extremely limited = 1
     Quite a bit limited = 2
     Moderately limited = 3
     Slightly limited = 4
     Not at all limited = 5
     Limited for other reasons or did not do = <missing value>

   - If at least three of Questions 1a-f are not missing, then compute

     Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

     (see footnote at end of this document for explanation of meaning of "actually answered")

2. Symptom Stability

   - Code the response to Question 2 as follows:

     Much worse = 1
     Slightly worse = 2
     Not changed = 3
     Slightly better = 4
     Much better = 5
     I've had no symptoms over the last 2 weeks = 3

   - If Question 2 is not missing, then compute

     Symptom Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

- Code responses to Questions 3, 5, 7 and 9 as follows:

  Question 3
  Every morning = 1
  3 or more times a week but not every day = 2
  1-2 times a week = 3
  Less than once a week = 4
  Never over the past 2 weeks = 5

3. Symptom Frequency (cont.)

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

7. Quality of Life (cont.)

   - If at least one of Questions 12, 13 and 14 is not missing, then compute

     Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

   - Code responses to each of Questions 15a-d as

     follows: Severely limited = 1
     Limited quite a bit = 2
     Moderately limited = 3
     Slightly limited = 4
     Did not limit at all = 5
     Does not apply or did not do for other reasons = <missing value>

   - If at least two of Questions 15a-d are not missing, then compute

     Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

   = mean of the following available summary scores: Physical Limitation Score
   Total Symptom Score Quality of Life Score Social Limitation Score

10. Clinical Summary Score

    = mean of the following available summary scores: Physical Limitation Score
    Total Symptom Score

Note: references to "means of questions actually answered" imply the following.
③ If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, calculate the mean of those questions as
(sum of the responses to those n-i questions) / (n-i)
not
(sum of the responses to those n-i questions) / n

If doing these calculations seems like too much trouble, consider using one of our tools – available at www.cvoutcomes.org:

- SAS or SPSS code
- Excel spreadsheets
- Web data services

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