2. SYNOPSIS

Study Centre(s)

This study was performed in 9 countries: Brazil (13 sites), Bulgaria (5 sites), Canada (6 sites), Hungary (10 sites), Poland (4 sites), Romania (4 sites), Russia (10 sites), Slovakia (4 sites) and the US (8 sites).

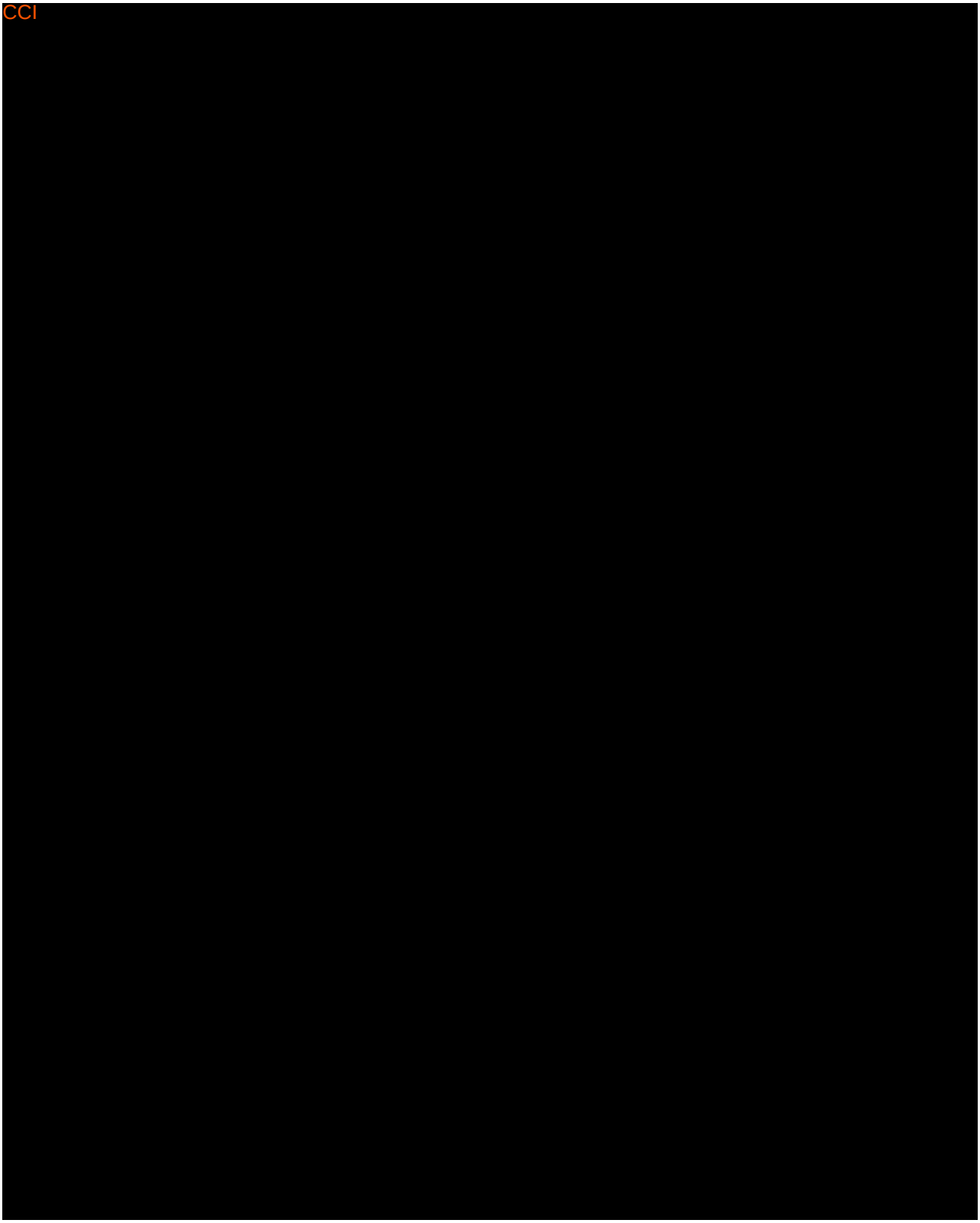
Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Endpoint/Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine if there is a difference between SZC and placebo in RAAS blockade treatment.	Proportion of patients 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	Safety	To evaluate the safety and tolerability of SZC in this patient population.	• Serious adverse events • Discontinuation of IP due to Adverse Events • Adverse Events • Changes in clinical laboratory parameters, including assessment of creatinine and renal function (eGFR). • Vital signs • Electrocardiogram
Safety	Safety	To explore whether SZC compared with placebo will affect the incidence of high and/or low S-K levels.	Number of patients and number of events with central laboratory levels of S-K: • > 6.0 mmol/L • > 5.5 mmol/L • < 3.5 mmol/L • < 3.0 mmol/L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In addition to the exploratory efficacy endpoints defined in the CSP, S-K was summarised over time as described in the SAP.

ACEi Angiotensin converting enzyme inhibitors; ARB Angiotensin receptor blockers; ARNI Angiotensin receptor blocker/neprolysin inhibitors; BP Blood pressure; CSP Clinical Study Protocol; CSR Clinical Study Report; eGFR Estimated glomerular filtration rate; HF Heart failure; IP Investigational Product; CCI lab-K Laboratory potassium; MRA Mineralocorticoid receptor antagonist; CCI CCI RAAS Renin-angiotensin aldosterone system; RAASi Renin-angiotensin aldosterone system inhibitor; SAP Statistical Analysis Plan; S-K Serum potassium; SZC Sodium zirconium cyclosilicate; CCI .

Study Design

This was an international, multicentre, parallel-group, randomised, double-blind, placebo-controlled Phase II study to evaluate the benefits and risks of using SZC to intensify RAASi therapy in patients with HF, in particular through the initiation and/or up-titration of MRA treatment, but also through up-titration of ACEi, ARB or ARNI therapy, without inducing clinically significant hyperkalaemia. Eligible patients were to have chronic HF (NYHA II-IV) and be mildly hyperkalaemic (S-K: 5.1 to 5.5 mmol/L) and/or be at high risk of developing hyperkalaemia. Patients were to be randomised in a 1:1 ratio (using an IVRS or IWRS) to receive SZC or placebo for 3 months while titrating RAASi therapies.

Of note, the study was paused from May to October 2019 to undergo a major protocol amendment. The subsequent CSP (CSP Version 4.0), included significant updates to the eligibility criteria, revised RAASi up-titration guidance and general updates to the study design. Further information is included in the relevant sections of the CSR.

The study was terminated prematurely because of the COVID-19 pandemic, and study procedures were modified to ensure patient safety and study integrity.

Target Patient Population and Sample Size

Adults (≥ 18 years of age) with an established and documented diagnosis of symptomatic HF with reduced ejection fraction (HFrEF; NYHA II to IV) which had been present for at least 3 months, who received treatment with an ACEi, ARB, or ARNI, and who had mild hyperkalaemia or were at risk of developing hyperkalaemia were eligible for participation. Patients were either taking no MRA or a low dose of MRA (spironolactone, eplerenone, or canrenone) defined as less than or equal to 12.5 mg qd or 25 mg qod. Patients also had LVEF of ≤ 40% within the past 12 months and eGFR 20 to 59 mL/min/1.73 m^2 at enrolment.

A sample size of 280 patients was considered to 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 patients per group provided 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 randomised patients.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Patients with S-K concentration as measured using the site's local laboratory (local lab-K) > 5.0 mmol/L at the last assessment before randomisation were randomised to receive SZC (AZD7270) 10 g or placebo 3 times daily for 2 days followed by SZC 5 g or placebo qd. Patients with local lab-K ≤ 5.0 mmol/L at the last assessment before randomisation were randomised to receive SZC 5 g qd or placebo qd. Prior to protocol version 4 (12 June 2019), an i-STAT device was used instead of local lab-K for enrolment and randomisation purposes.

Placebo and SZC were administered orally. Study drug was to be up- or down-titrated depending on the administered dose of study drug and the local lab-K at every study visit.

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Duration of Treatment

Patients received SZC or placebo for up to 3 months while titrating RAASi therapies. During the study interruption, and in case of early study discontinuation due to COVID-19, patients were called to attend the EoT visit (Visit 8) prematurely.

Statistical Methods

- The efficacy analyses were based on the Full analysis set that included all randomised patients. The safety analyses were based on the Safety analysis set, which was a subset of the Full analysis set that included only the patients who received at least one dose of study drug.
- The primary objective of detecting a difference in the distribution of RAASi medication between the 2 treatment groups at 3 months post randomisation was evaluated by comparing the number of patients in the following categories: "No, or less than target dose, ACEi/ARB/ARNI and no MRA", "ACEi/ARB/ARNI at target dose and no MRA", "MRA at less than target dose" and "MRA at target dose". The null hypothesis of no difference between the treatment groups in the number of patients in these categories was tested at 5% level of significance. Multiple imputation was performed to mitigate the impact of the missing data. For each of the imputed data sets, a Chi-square test was performed, with the corresponding test statistics then pooled and used in an F-test according to Ratitch et al 2013.
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- Safety was evaluated by summarising, and listing, AEs (including DAEs, SAEs and SAEs with death as the outcome). The evaluation included a tabulation by SOC and PT, by intensity and causality. Laboratory measurements, as well as vital signs and ECG findings, were also summarised, in a descriptive manner, and listed. Separate analyses were performed to evaluate the occurrence of oedema and hypokalaemia.

Patient Population

A total of 379 patients were enrolled, of which 182 patients were randomised. Of the 182 patients who were randomised (SZC: 92 patients, placebo: 90 patients), the majority completed the study (SZC: 90 patients [97.8%], placebo: 86 patients [95.6%]). Patients who completed the study early/completed the EoT visit early due to the Sponsor's decision to prematurely terminate the study because of the COVID-19 pandemic were considered to have completed.

All but one of the randomised patients received treatment (SZC: 91 patients [98.9%], placebo: 90 patients [100.0%]) and over half completed the intended 3 months of treatment (SZC: 57 patients [62.0%], placebo: 51 patients [56.7%]). The most common reason for premature discontinuation of treatment was the Sponsor's decision to prematurely terminate the study due to the COVID-19 pandemic (SZC: 19 patients [20.7%], placebo: 26 patients [28.9%]).

Of the 182 patients randomised, all were included in the Full analysis set. All patients who took at least one dose of study drug were included in the Safety analysis set; 1 patient in the SZC group was excluded as the patient did not take any study drug.

Overall, the majority of patients in the Full analysis set were White (179 patients [98.4%]) and most patients were male (108 patients [59.3%]). The mean age was 71.9 years and the most common age group was 65 to 84 years (134 patients [73.6%]). Mean potassium and LVEF at baseline were 4.86 mmol/L and 33.8%, respectively. Most patients were NYHA class II (64.8%) and had an eGFR of > 20 to ≤ 45 mL/min/1.73 m^2 (62.1%). The country that enrolled the most patients was Russia (63 patients [34.6%]) followed by Hungary (31 patients [17.0%]).

The demographic and baseline characteristics were generally balanced between the treatment groups. The minor imbalances found in age group (≥ 85 years) and some pre-exiting conditions were not expected to affect the efficacy and safety evaluations. The study was affected by the COVID-19 pandemic and the study was prematurely terminated resulting in a reduced sample size (182 patients as opposed to the planned 280 patients) and a high premature treatment discontinuation rate due to the COVID-19 pandemic (24.7%). However, there were no COVID-19 related concerns about the overall quality of the data collected during the study and no COVID-19 related safety concerns.

Summary of Efficacy Results

Results for the primary efficacy endpoint and sensitivity analyses of the primary analysis are summarised in the table below.

Table S2 Objectives and Outcome Variables

	Difference of proportion of subjects in each RAASi use category at 3 months (SZC - Placebo)				
	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**	**p-value**
Primary analysis (multiple imputation)	1.2%	-0.4%	-10.3%	9.4%	0.426
Sensitivity analysis (no imputation)	1.6%	-4.9%	-9.4%	12.8%	0.353
Sensitivity analysis (last value carried forward)	-0.4%	-0.4%	-9.3%	10.0%	0.419
Sensitivity analysis (COVID-19)	1.1%	-0.4%	-9.1%	8.3%	0.619

Source: Table 14.2.

Primary analysis and sensitivity analysis from CSR Tables 14.2.1.1, 14.2.1.2, 14.2.1.3 and 14.2.1.4.

p-values for Primary analysis and COVID-19 sensitivity analysis were obtained by pooling the p-values from Chi-square tests performed on individual data sets and reflects a global test of no difference in distribution of subjects in the respective categories between SZC and placebo groups.

Note: The COVID-19 sensitivity analysis was performed restricting results to only those obtained prior to the onset of the COVID-19 pandemic (ie, prior to 11 March 2020).

The COVID-19 sensitivity analysis also uses the multiple imputation procedure for imputing missing values.

ACEi Angiotensinogen converting enzyme inhibitors; ARB Angiotensin receptor blockers; ARNI Angiotensin receptor blocker and neprolysin inhibitors; COVID-19 Coronavirus disease 2019; MRA Mineralocorticoid receptor antagonist; RAASi Renin-angiotensin aldosterone system inhibitor; SZC Sodium zirconium cyclosilicate.

- There was no statistically significant difference between SZC and placebo in the distribution of proportion of patients in the RAASi treatment categories at 3 months ($p = 0.426$); however, the SZC group had a numerically higher proportion of patients at target MRA dose compared with the placebo group (56.4% and 47.0%, respectively). Sensitivity analyses were consistent with the primary analysis.

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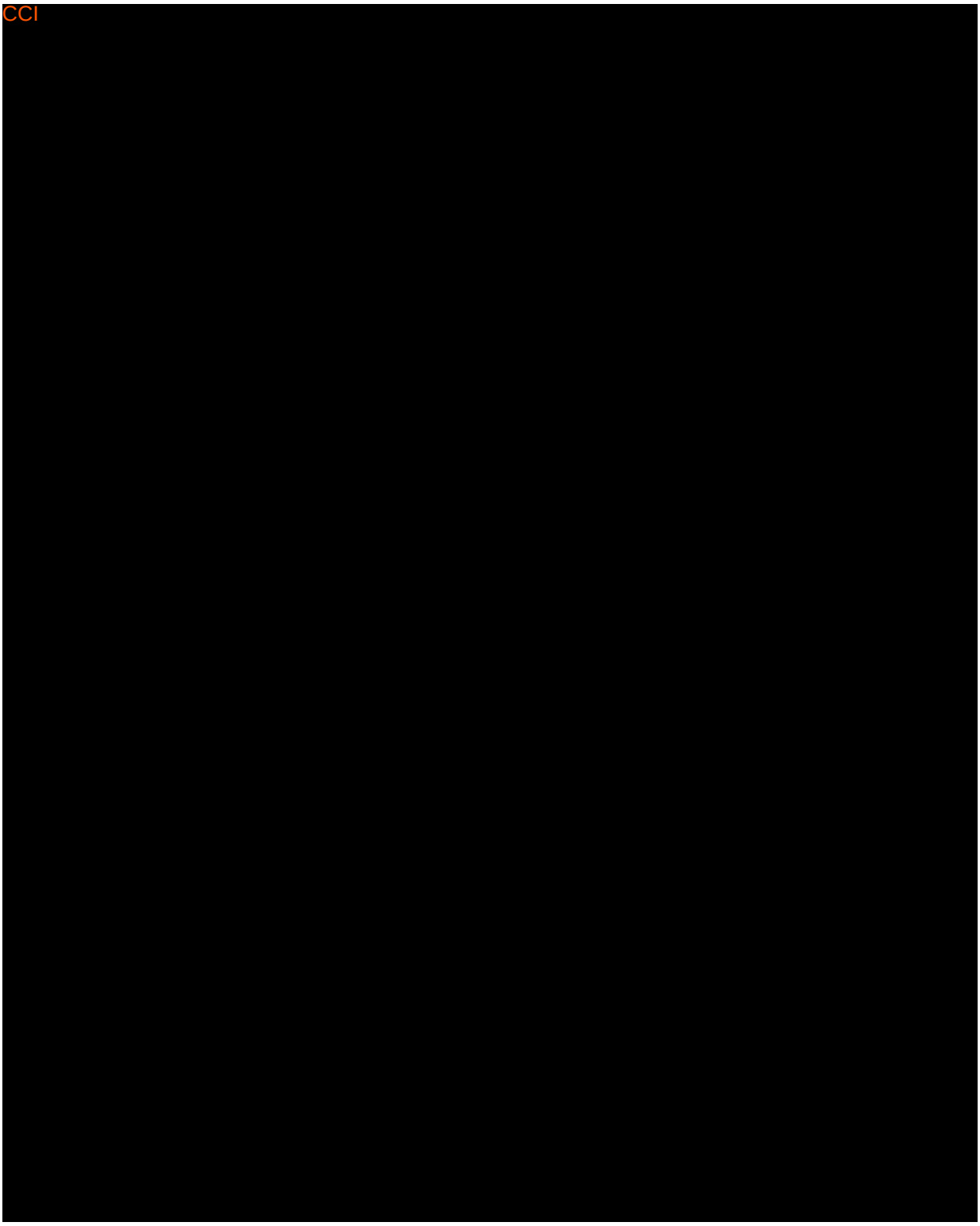
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Summary of Safety Results

- Duration of exposure was similar between the SZC and placebo groups (mean duration of exposure was 65.9 and 64.0 days, respectively; median duration of exposure was 80.0 and 77.5 days, respectively).
- Overall, SZC was well tolerated in the population studied. The key observations were:
  - Forty-three (47.3%) and 47 patients (52.2%) in the SZC and placebo groups, respectively, reported an AE during the study. The most commonly reported events in the SZC group by MedDRA PT were cardiac failure chronic, chronic kidney disease and viral upper respiratory tract infection and in the placebo group were cardiac failure chronic, chronic kidney disease, viral upper respiratory tract infection and nasopharyngitis. Most AEs were mild or moderate in intensity and the incidence of AEs that were considered related to study drug by the Investigator was low and comparable between the treatment groups.
  - One patient (1.1%) in each treatment group died during the study, both causal events were cardiac disorders; neither event was considered related to study drug by the Investigator.
  - The incidence of SAEs (SZC: 14 patients [15.4%], placebo: 10 patients [11.1%]) and DAEs (SZC: 5 patients [5.5%], placebo: 2 patients [2.2%]) was comparable between the treatment groups.
  - One SAE (generalised oedema in the SZC group) was considered related to study drug by the Investigator; this event (along with a concurrent AE of cardiac failure chronic) occurred following an accidental overdose of SZC (see Section 12.1 of the CSR) and led to discontinuation of study drug. The only other DAE considered related to study drug by the Investigator was nausea, reported for 1 patient in the SZC group.
  - The incidence of oedema related AEs was low (SZC: 3 patients [3.3%], placebo: 1 patient [1.1%]).
  - During the study, numerically more patients in the SZC group (11 patients [12.1%]) had events of cardiac failure compared with the placebo group (5 patients [5.6%]); of these, 9 patients (9.9%) and 4 patients (4.4%), respectively, reported events while on-treatment. Most events were mild or moderate in severity, did not change the dose of study drug and all were resolved by the end of the study, with the exception of 1 event that was resolving. The incidence of serious cardiac failure events during the study was low and comparable between the treatment groups (SZC: 4 patients [4.4%], placebo: 3 patients [3.3%]); of these, 2 patients (2.2%) in each treatment group reported serious events while on-treatment.
  - With the exception of S-K, evaluation of clinical laboratory variables including eGFR revealed no clinically meaningful differences between the 2 treatment groups. No patients met the criteria for a potential Hy's Law case.
  - During the study, no patients in either treatment group had a central laboratory S-K value of < 3.0 mmol/L. Seven patients (7.7%) in the SZC group had low (< 3.5 mmol/L) S-K values compared with 0 patients in the placebo group.

- During the study, 57 patients (62.6%) in the SZC group and 69 patients (76.7%) in the placebo group had high (> 5.0 mmol/L) central laboratory S-K values. Of these, 3 patients (3.3%) and 4 patients (4.4%) in the SZC and placebo groups, respectively, had S-K values of > 6.0 mmol/L and 2 patients (2.2%) and 3 patients (3.3%), respectively, had S-K values of > 6.5 mmol/L.
- Evaluation of vital signs (including diastolic and systolic BP) and ECG data revealed no clinically meaningful differences between the 2 treatment groups.

Conclusion(s)

- In this study that was terminated prematurely due to COVID-19, there was no statistically significant difference between SZC and placebo in the proportion of patients meeting RAASi treatment categories at 3 months (p = 0.426).
  - Numerically more patients were observed with MRA target dose at 3 months in the SZC group compared with the placebo group (56.4% and 47.0%, respectively).
  - Sensitivity analyses were consistent with the primary analysis.
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- Numerically more patients in the SZC group developed worsening of HF during the study compared with the placebo group. However, the total number of cases was small, the number of patients with serious events was similar between the treatment groups, and the data obtained were not indicative of an increased risk of worsening of HF related to treatment with SZC.
- SZC was well tolerated and no new safety concerns in this patient population with HF and CKD were raised.