Clinical Study Protocol	
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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)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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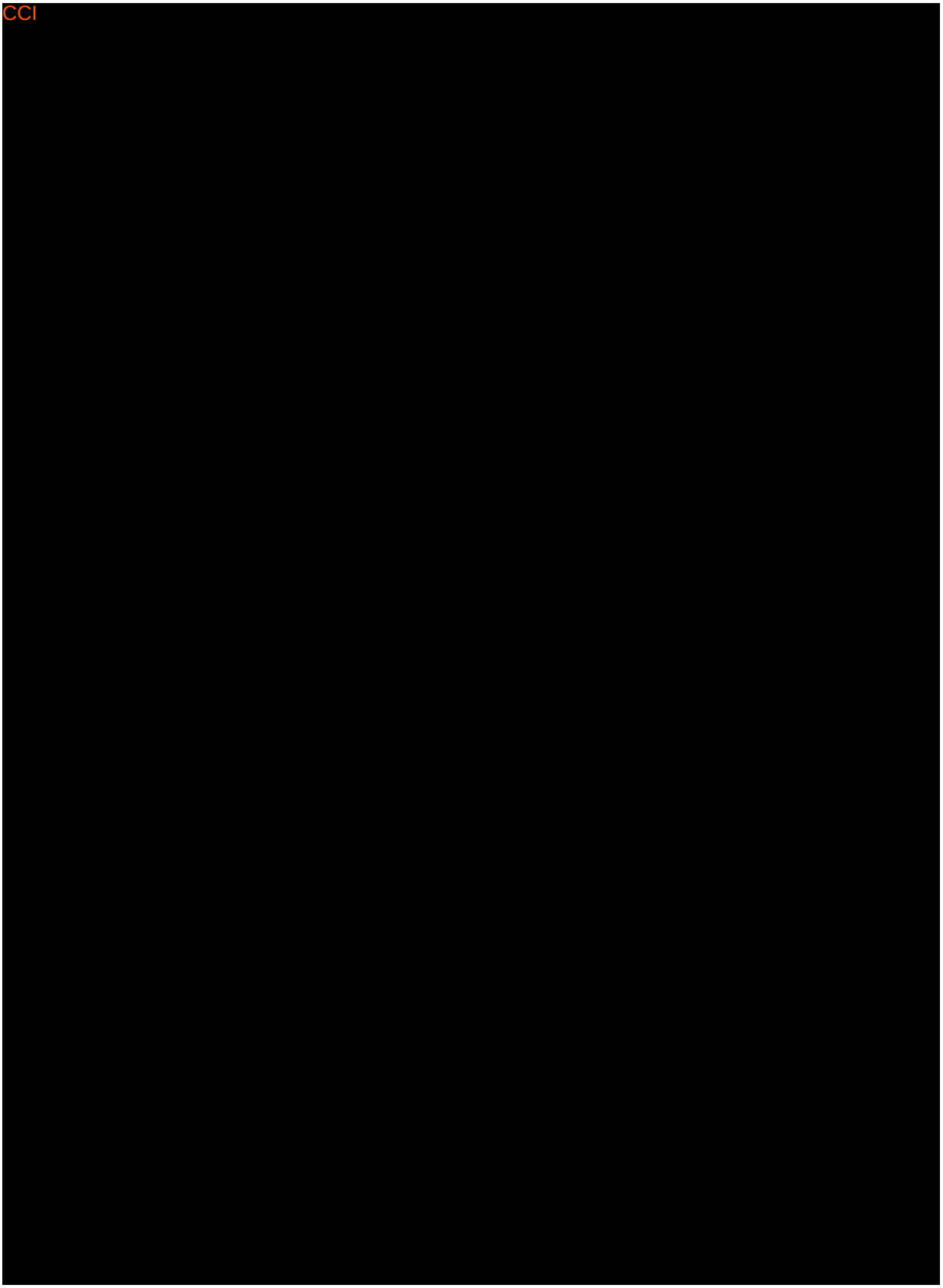
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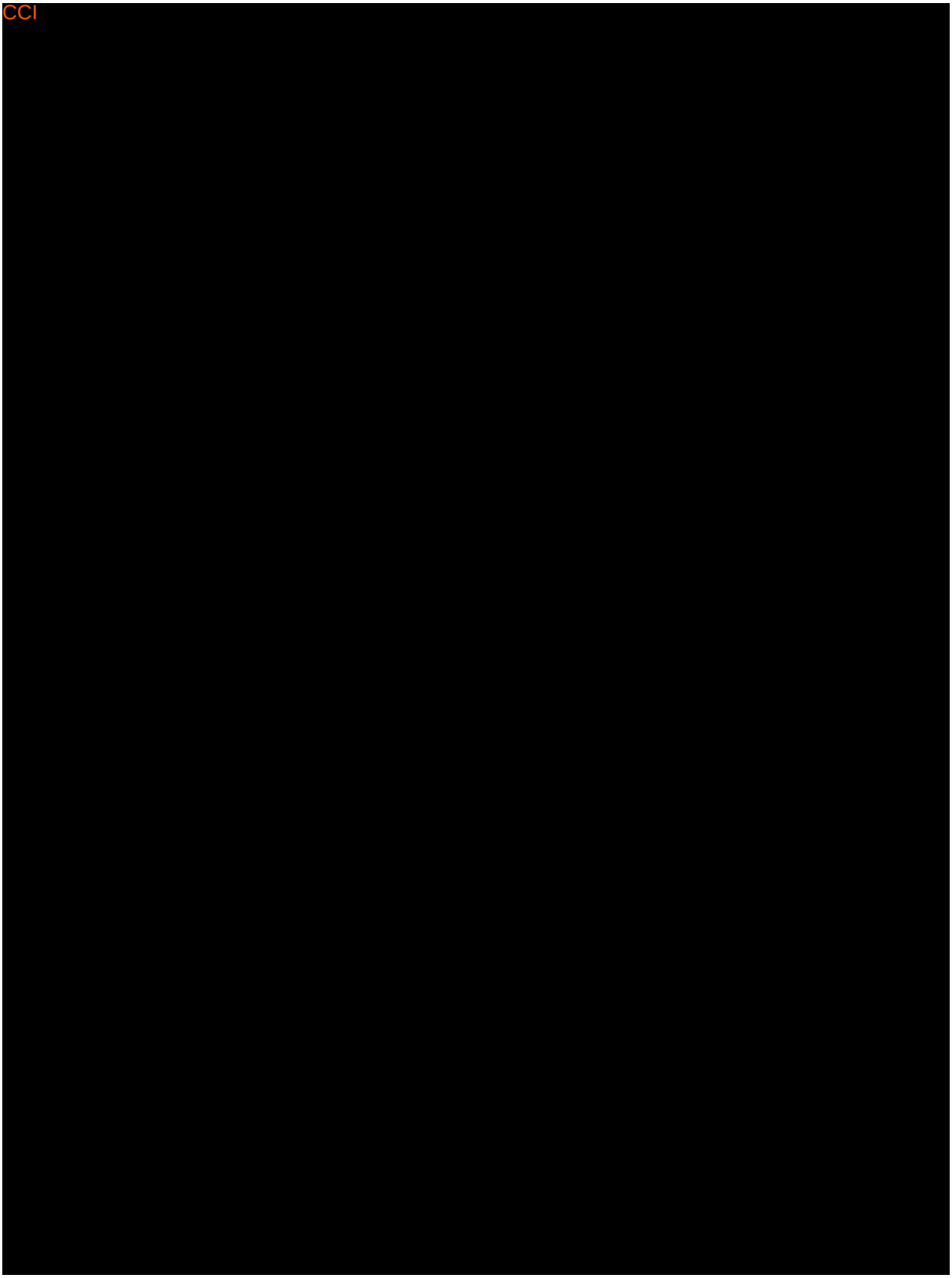

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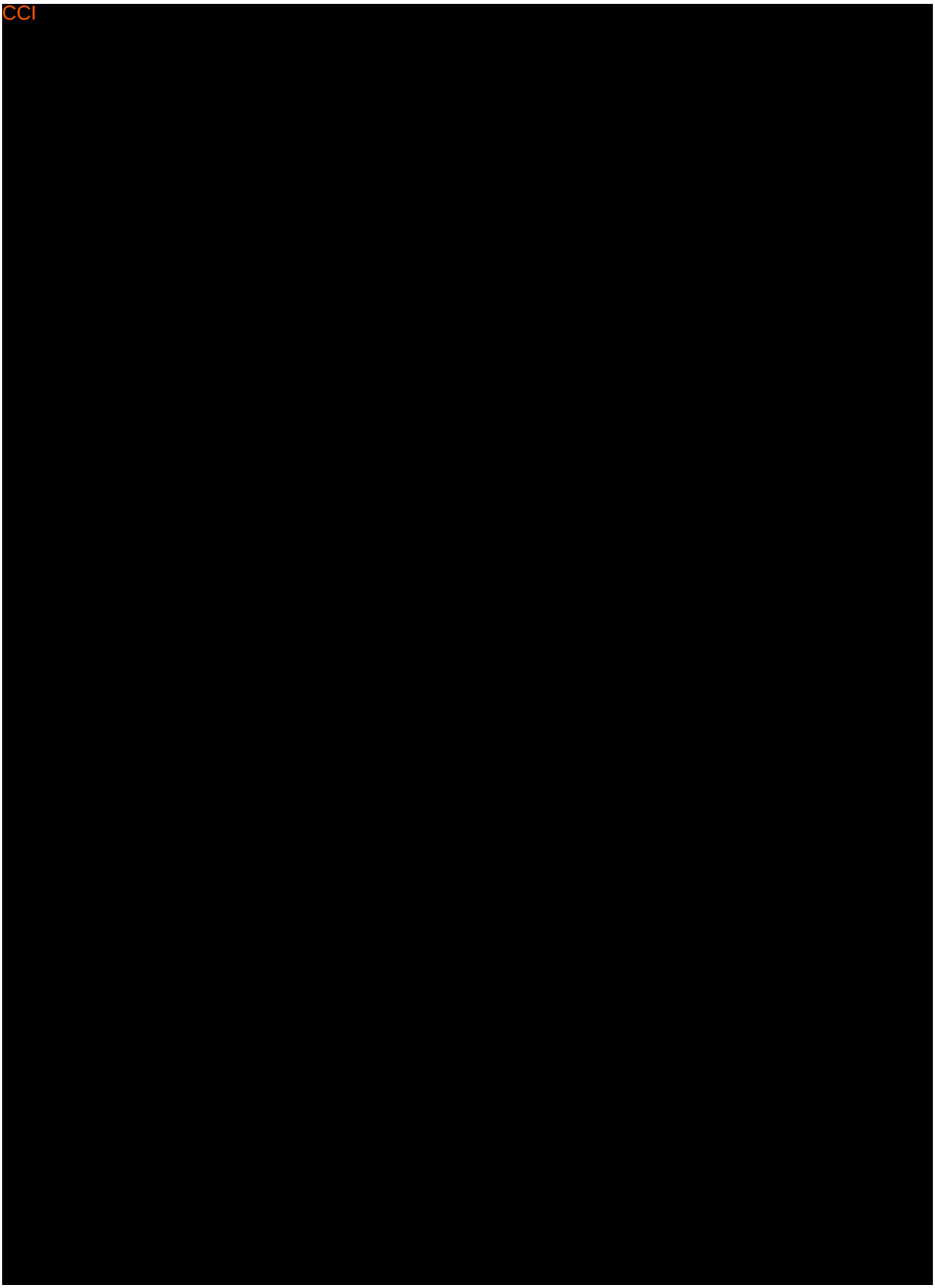

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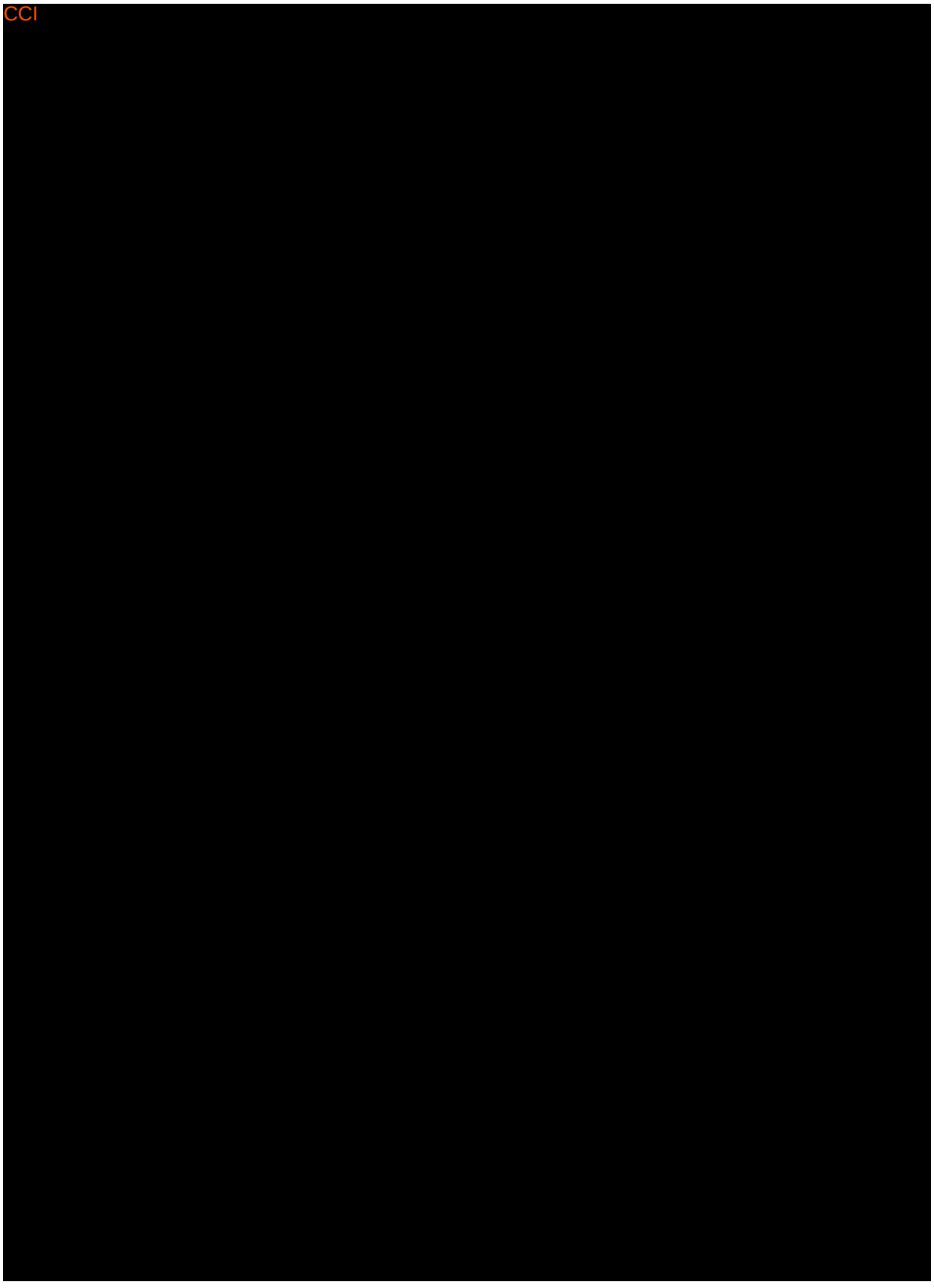

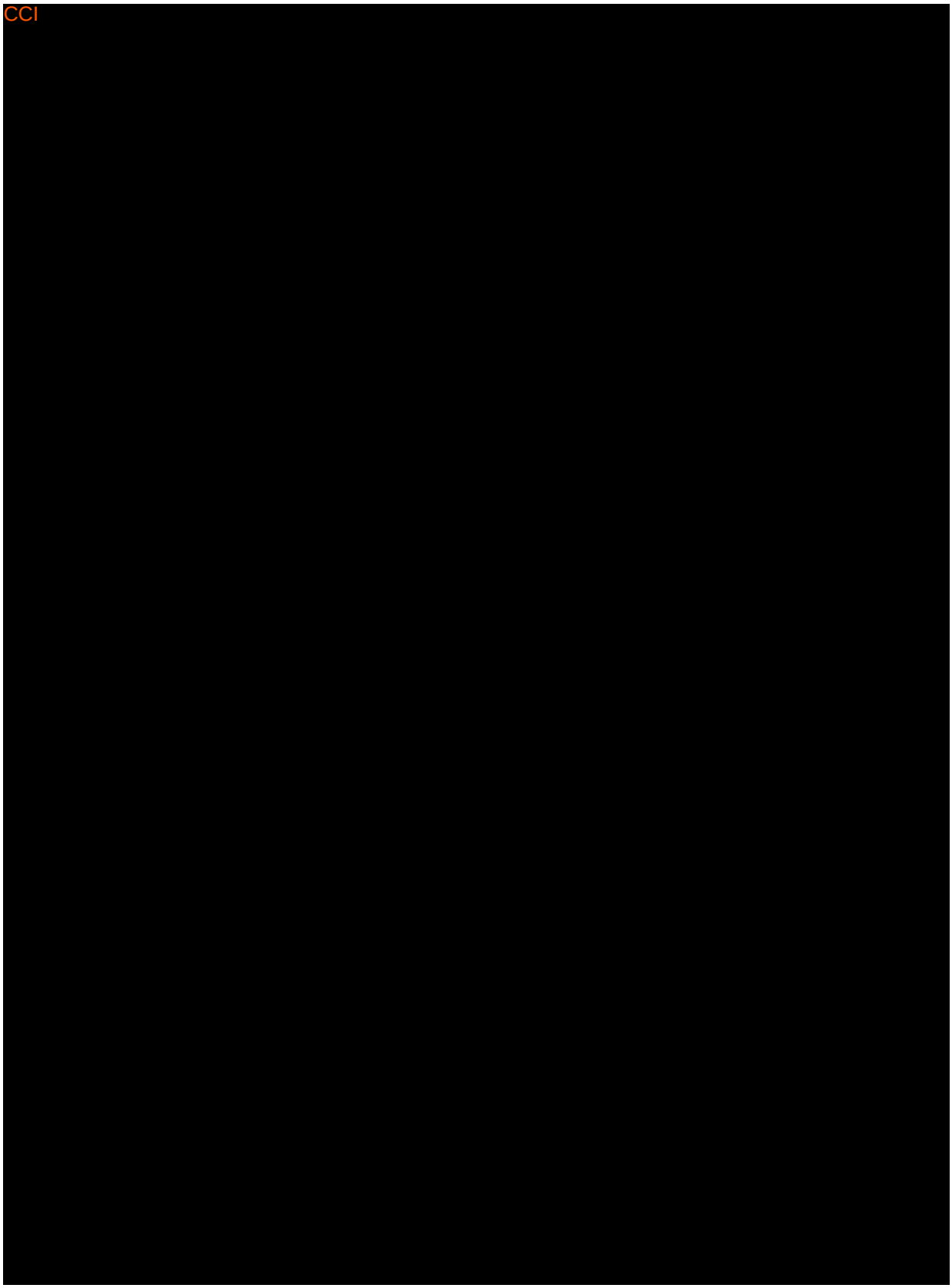
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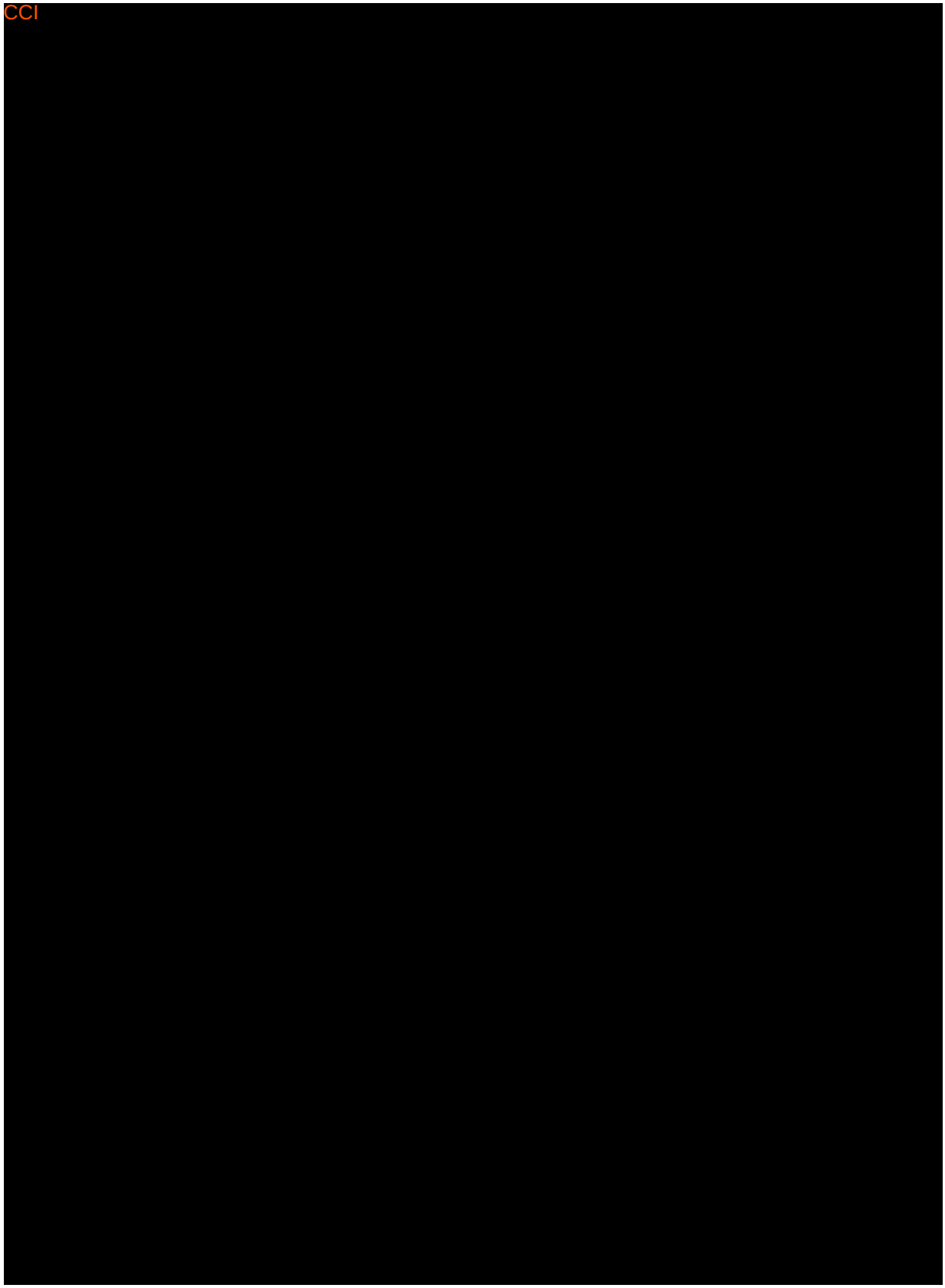
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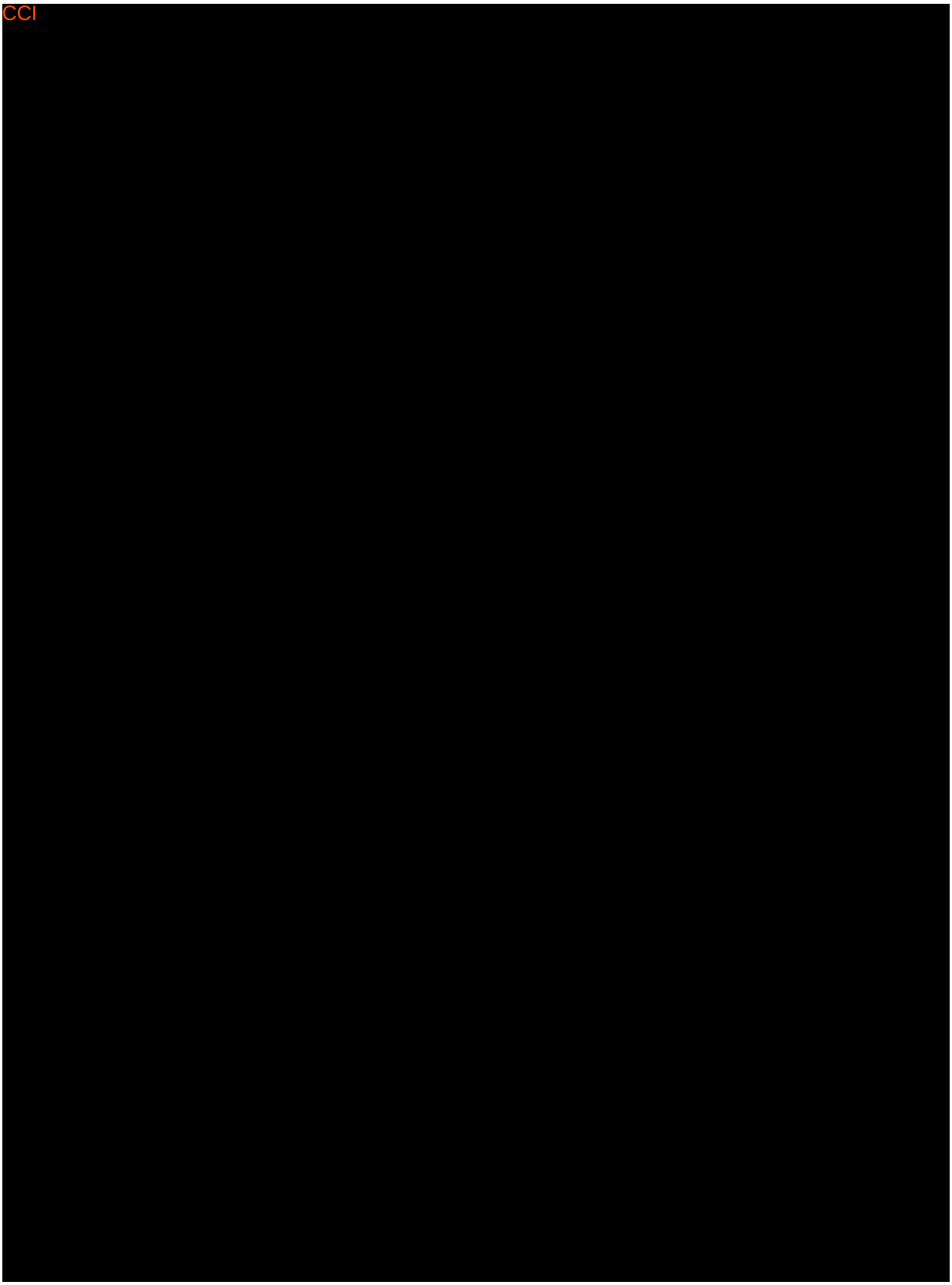

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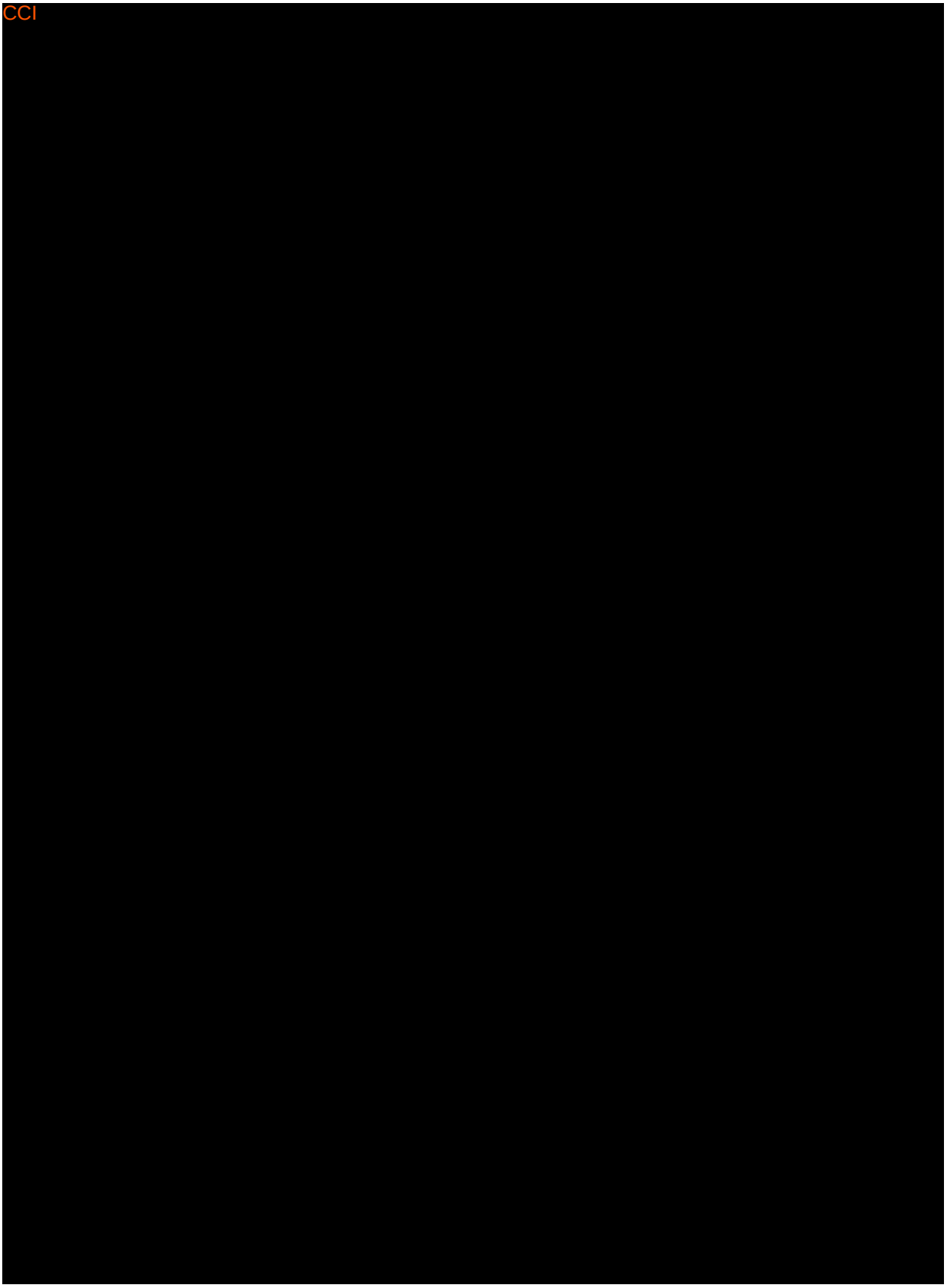

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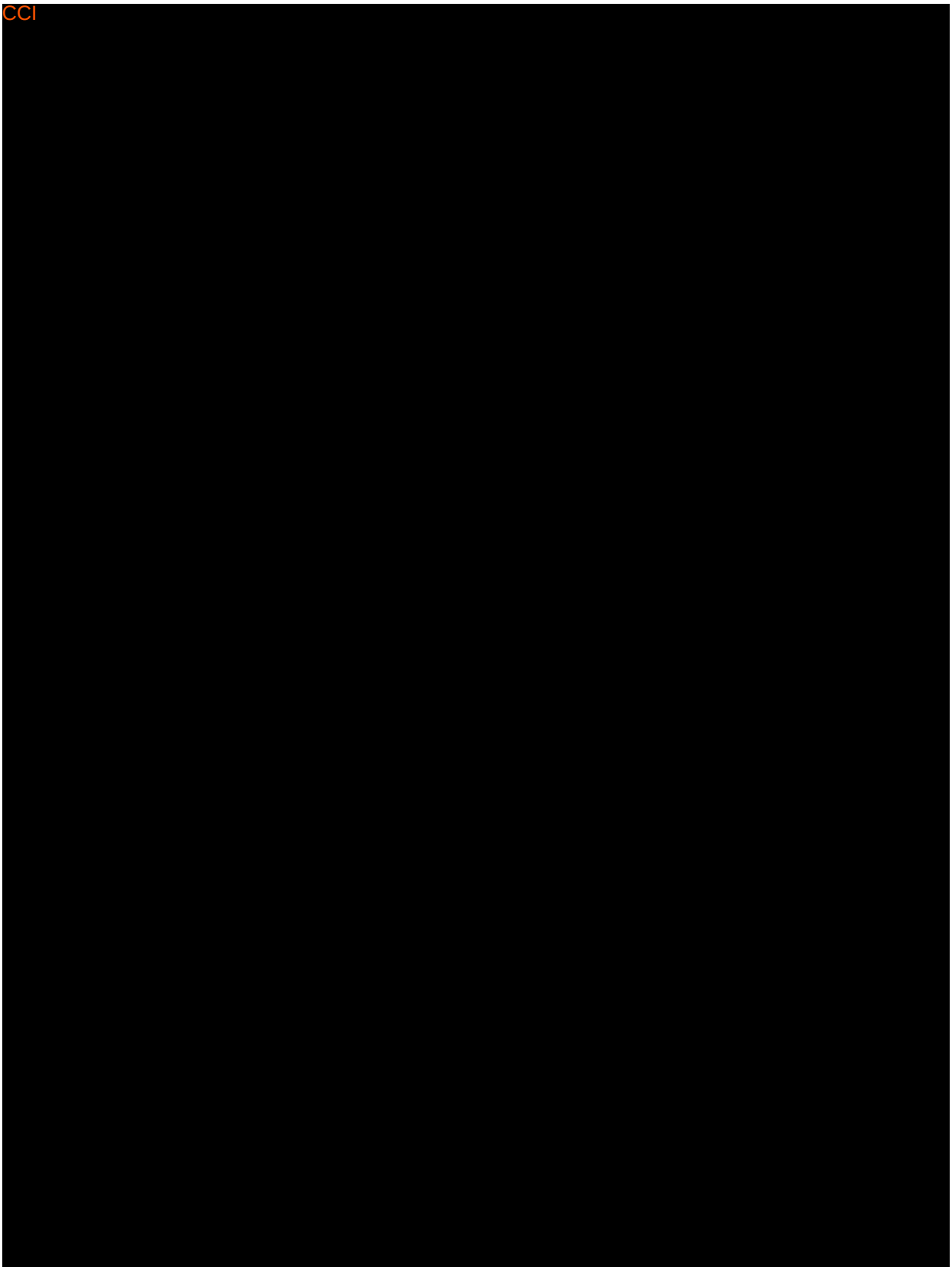

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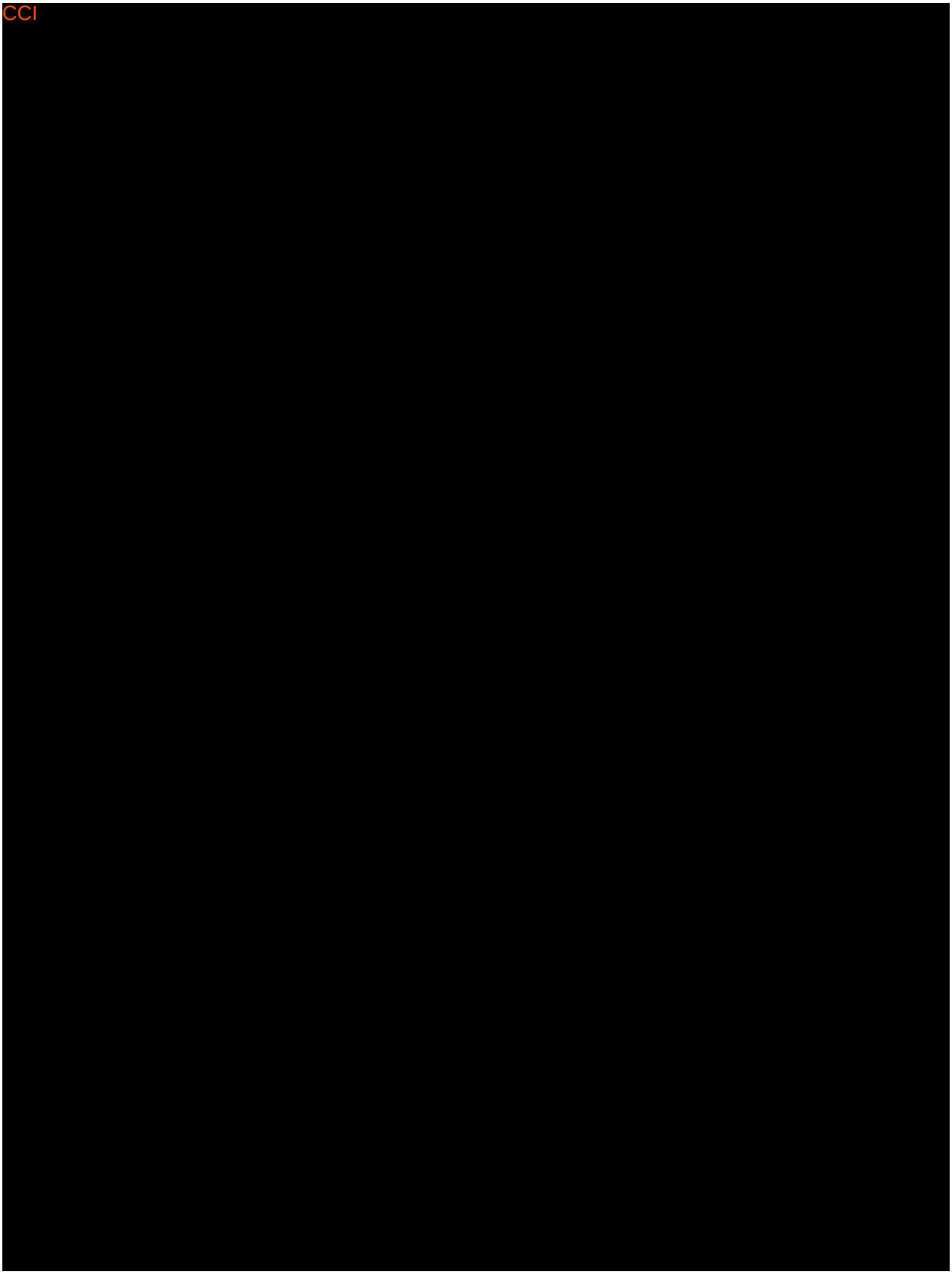

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy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

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1.1 Schedule of Activities (SoA)

Table 1 Study Assessments

Visit	**1*** **(Screening)**	**2***	**3**	**4**	**5**	**6**	**7**	**8 (EoT)**	**9**	**10**	**Dose change for either RAASi or IP**	**Details in CSP section or Appendix**
Week (Day 1 of)	**-2 to 1**	**1**	**2**	**3**	**5**	**7**	**9**	**13**	**14**	**17**		
Day	**-14 to 1**	**1**	**8**	**15**	**29**	**43**	**57**	**85$**	**92 (or 7d after last IP)$**	**115 (or 30d after last IP)$**	**7d after every titration (±2) / 3d after MRA initiation (±1)**	
Window	**-14 to 1**		**±2**	**±3**	**±3**	**±7**	**±7**	**±7**	**±2**	**±7**		
Informed consent	X											Section 5.1
Inclusion /exclusion criteria	X	X										Sections 5.1 and 5.2
Routine clinical procedures												
Demography	X											Section 8.10
Physical examination	X											Section 8.2.2
Targeted physical examination		X	X	X	X	X	X	X	X	X	X	Section 8.2.2
Medical history and comorbid conditions	X											Section 5.1
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
NYHA class	X	X						X		X		Section 8.1.4
Height	X											Section 8.2.2
Weight	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.2
ECG	X							X		X		Section 8.2.4

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Window	**-14 to 1**		**±2**	**±3**	**±3**	**±7**	**±7**	**±7**	**±2**	**±7**		
Concomitant medication	At every visit and may be conducted by phone if not tied to a visit.											Section 6.5
Routine safety measurements												
Adverse events	At every visit and may be conducted by phone if not tied to a visit.											Section 8.3
Pregnancy test (serum or urine)	X									X		Section 5.1
Safety laboratory assessments (central)	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1
Local lab potassium and creatinine#	X	X	X	X	X	X	X	X	X	X	X	Sections 8.2.1 and 8.1.2
Biomarker analyses												
Biomarker blood sample collection		X	X					X		X		Section 8.8
Morning spot urine			X					X				Section 8.1.5
PRO measurements												
KCCQ		X						X		X		Section 8.1.3.2
PGIC								X				Section 8.1.3.1
Pharmacogenetic sampling (optional)												
Blood sample		X										Section 8.7
Study treatment administration and procedures												
Randomisation		X										Section 6.3
Study treatment dispensed		X			X		X					Section 6

Visit	**1*** **(Screening)**	**2***	**3**	**4**	**5**	**6**	**7**	**8 (EoT)**	**9**	**10**	**Dose change for either RAASi or IP**	**Details in CSP section or Appendix**
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Window	**-14 to 1**		**±2**	**±3**	**±3**	**±7**	**±7**	**±7**	**±2**	**±7**		
Study treatment returned					X		X	X				Section 6
ZS / placebo titration			X	X	X	X	X				X	Section 6.7
ACEi/ARB/ARNI/ MRA titration			X	X	X	X	X		X	X	X	Section 6.5.1
ACEi/ARB/ARNI/ MRA to baseline or lowest dose								X				Section 6.5.1

* Visits 1 and 2 may be combined into one visit. It is acceptable to have a 24-hour window between the local lab draw and the rest of the visit procedures. When V2 occurs within one calendar day after V1, it will still be considered a single combined visit. In this case, Investigators should ensure no other entry criteria (e.g., medications) have changed from V1 to V2.

Data results from local lab samples should be obtained as soon as possible after sample collection, but no later than 24 hours after the sample collection. If blood samples for local lab are taken at the study visit and the results are not known prior to the subject leaving the visit, the investigator may call the subjects or bring them back the following day for instructions regarding concomitant medication titration and IP dosing. Alternatively, if more feasible for the subject and investigator, blood samples for the local lab may be collected one day before study procedure in cases when the local lab sample analysis time is expected to be longer than the duration of the subject's clinic visit. $ While the intention was for all subjects enrolled under Amendment 3 to have all study visits in order, despite any premature IP discontinuation, the COVID-19 pandemic necessitated some patients skipping ahead to an early termination visit with Visit 8 procedures performed (See Appendix I). In these cases, the investigator unblinded the patients for medical management, and the 7-day and 30-day safety follow visits were performed relative to the date Visit 8 occurred. An additional potassium measurement was also recommended 48 hours post-last IP dose for patients on active IP or with large RAASi changes. Note this skipping ahead to Visit 8 and unblinding for some patients during the COVID-19 pandemic is similar to the procedures followed for patients enrolled during Amendments 1, 2, and 3.

1.2 Synopsis

International co-ordinating investigator: Jean-Claude Tardif

Protocol Title:

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)

Short Title:

PRIORITIZE HF

Rationale:

Heart failure (HF) patients are frequently not administered renin-angiotensin aldosterone system inhibitor (RAASi) therapies at recommended doses due to hyperkalaemia, despite proven mortality and morbidity benefits. Sodium zirconium cyclosilicate (ZS) is a novel non-absorbed potassium trap proven to lower serum potassium (S-K) and maintain normokalaemia. The purpose of PRIORITIZE HF is to assess if a treatment regimen containing ZS will allow RAASi therapies to be up-titrated to target doses in patients with heart failure and elevated serum potassium or at high risk of developing elevated serum potassium.

Study Objectives

Primary Objective:	**Endpoint/Variable:**
To determine if there is a difference between ZS 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 ZS 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 • ECGs
To explore whether ZS 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 ZS 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 ZS 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 ZS 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 ZS and placebo in 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 is defined in the Statistical Analysis Plan.
To explore change of blood pressure (BP) in the ZS 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 ZS 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 ZS group compared with the placebo group.	Change in NYHA class from baseline.
To explore the effect of treatment with ZS 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 ZS	Changes in biomarkers N-terminal pro b-type natriuretic peptide (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).

Overall 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 (ZS) to initiate and 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 ZS or placebo for 3 months while titrating RAASi therapies.

COVID-19 Pandemic Modifications Summary: The study was terminated prematurely because of the COVID-19 pandemic, and study procedures were modified to ensure patient safety and trial integrity. The full details of these changes, in addition to their impact, can be found in Appendix I.

Specifically, as of April 01, 2020, all sites were asked to discontinue patients from the active treatment phase of the study. Sites were told to bring forward all patients who had not yet completed Visit 8 (End-of-Treatment visit) to conduct Visit 8 as soon as possible. At the end of Visit 8, sites were requested to withdraw the IP, and unblind each patient to the IP via the IVRS/ **IWRS** system. For patients on placebo, the patients should have been managed as deemed appropriate by the investigator. For the patients on Lokelma, patients should have been RAASi down-titrated to pre-randomization (or lowest) doses, and potassium should have been checked at 48 hours and also 7 days post IP discontinuation. Visit 9, a safety follow-up visit 7 days after IP discontinuation, should have been conducted for all patients.

Study Period:

Date of first subject enrolled: 26 June 2018

Estimated date of last subject completed: Q2 2020

Number of Subjects:

Approximately 280 subjects were planned to be randomized, but due to the premature termination, 182 patients were randomized..

Treatments and treatment duration:

As detailed in the Schedule of Activities (SoA) above, subjects signing informed consent will be screened for up to 14 days. Patients meeting the inclusion criteria, but not the exclusion criteria, are then randomized and start study therapy. It is allowed to perform all screening activities at a single visit, allowing subjects to be screened and randomized at a single visit.

Study treatment in this study refers to ZS or placebo, while RAASi therapies are considered background therapy and will not be provided by the study sponsor. Note that sodium zirconium cyclosilicate can be abbreviated as either ZS or SZC in documents and refer to the same product.

Patients with serum potassium concentration as measured using the site's local lab (local lab-K) >5.0 mmol/L at the last assessment before randomization will be randomized to receive ZS 10 g or placebo three times a day (tid) for 2 days followed by ZS 5 g or placebo once a day (qd). Patients with local lab-K $\leq$ 5.0 mmol/L at the last assessment before randomization will be randomized to receive ZS 5 g qd or placebo qd. The total treatment duration will be

approximately 12 weeks. Also, ZS / placebo will be up / down titrated in the range ZS 5 g every other day (qod) to ZS 15 g qd (or matching doses of placebo) to maintain the subject in the normokalaemic range (S-K 3.5 to 5.0 mmol/L inclusive) during the randomized treatment period.

During the randomized treatment period the RAASi therapy will be up-titrated, if possible, depending on local lab-K and other laboratory and clinical parameters. RAASi therapy should be uptitrated in patients with local lab-K $\leq$5.0 mmol/L; in patients with local lab-K > 5.0 uptitration may be attempted when potassium levels are moving towards normal, e.g. upon Investigational Product (IP) dose increase.

Up-titration of RAASi therapy means increasing the dose of ACEi/ARB/ARNI to a target dose or a maximum tolerated dose AND adding or uptitrating a mineralocorticoid receptor antagonist (MRA) and titrating the MRA to a target/maximum tolerated dose (Table 5). Refer to Section 6.5.1 for specific details.

Patients will participate in the study for approximately 16 to 18 weeks in total, depending on the duration of the screening period.

Data Monitoring Committee (DMC):

A data monitoring committee (which can also refer to a Safety Review Committee) will be established to review emerging safety data. See Appendix A for details.

Statistical methods

The primary analysis to determine if there is a difference between ZS and placebo in RAAS blockade treatment will be performed using the Full analysis set. The null hypothesis is that there is no difference between treatments in the distribution of proportion of patients in the RAAS blockade treatment categories, and the alternative hypothesis is that there is a difference. The hypothesis will be tested at a significance level of 5% using a chi-square test for homogeneity.

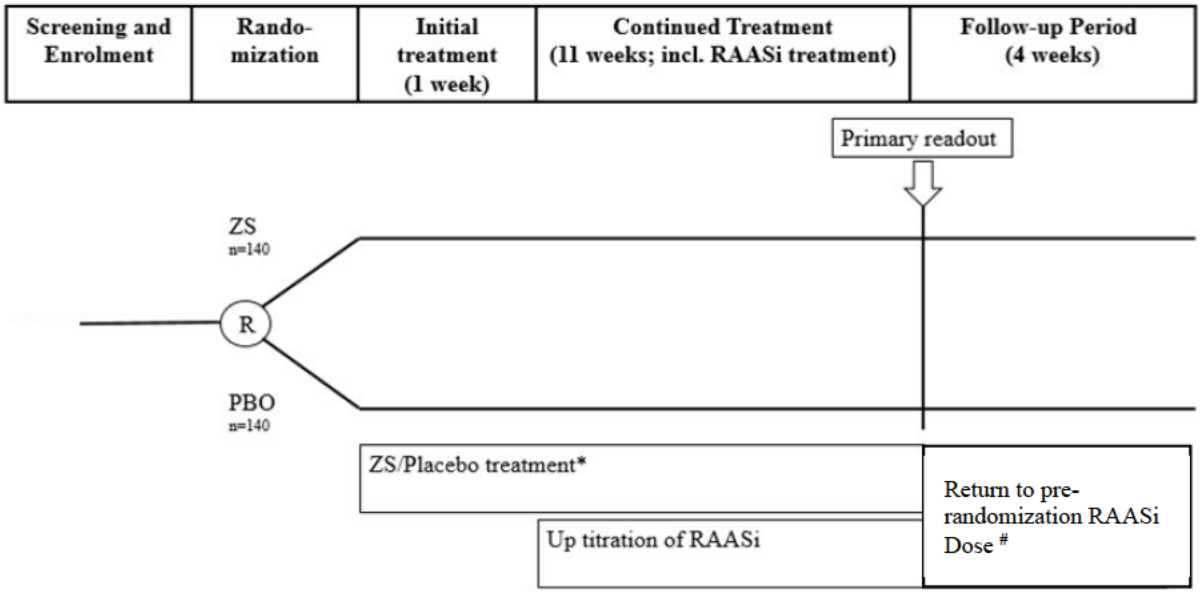
The study will employ a 1:1 randomization scheme. A sample size of 280 subjects will allow for estimation of the effect in the primary objective. Due to lack of prior knowledge of the distribution in the placebo group, the following considerations were made with regards to sample size. Assuming a difference 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 premature termination, 182 patients were randomized.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



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

2. INTRODUCTION

2.1 Study rationale

HF patients are frequently not administered RAASi therapies at recommended doses due to hyperkalaemia or fear of hyperkalaemia. Sodium zirconium cyclosilicate (ZS) is a novel non-absorbed potassium trap proven to lower S-K and maintain normokalaemia. The purpose of PRIORITIZE HF is to assess if a treatment regimen containing ZS will allow RAASi therapies to be up-titrated to target doses without inducing clinically significant hyperkalaemia.

2.2 Background

Despite advances in management and treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF), HF continues to be a major cause of mortality, initial and recurrent hospitalizations, and suboptimal quality of life. The prevalence and incidence of HF continues to increase globally. An estimated 38 million people are affected by HF worldwide (Braunwald 2015) with over 1 million hospitalizations annually in the United States and

Europe (Ambrosy et al 2014). The annual global economic burden in 2012 was estimated to be $108 billion (Cook et al 2014) and is projected to increase dramatically as the population ages.

The current treatment paradigm for HF involves the simultaneous targeting of multiple pathways including the renin-angiotensin-aldosterone system (RAAS), the autonomic system, and symptomatic treatment with diuretics.

Even with the best possible treatment, the five-year survival rate for HF is worse than for most cancers (Braunwald 2015). For patients with chronic HF, worsening symptoms require prompt medical attention, add to the burden of hospital and non-hospital settings and also have a considerable economic impact (Ponikowski et al 2016, Okumura et al 2016).

Inhibition of the RAAS using RAAS inhibitors (RAASi) has been proven to provide survival benefits for patients with HF. RAASi drug classes include angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), combined angiotensin receptor / neprolysin inhibitors (ARNI), and mineralocorticoid receptor antagonists (MRA).

International HF guidelines from American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend administration of one ACEi, ARB or ARNI, and one MRA to patients with HFrEF and ejection fraction <40% (Ponikowski et al 2016, Yancy et al 2017). Unfortunately, a significant proportion of patients do not receive ACEi/ARB/ARNI and/or MRA treatments as recommended, or do not receive the treatments at the recommended doses, frequently due to fear of hyperkalaemia (Epstein et al 2016).

The prevalence of hyperkalaemia has been reported to be 3-4% in hospitalized patients, and the risk is considerably increased in persons with advanced chronic kidney disease, heart failure, diabetes and/or treatment with RAASi (Einhorn et al 2009, Fleet et al 2012, Kovesdy 2015). Hyperkalaemia often presents without symptoms or with nonspecific symptoms including malaise, confusion, muscle weakness or signs of cardiac arrhythmias (Henneman et al 2016). Even mild elevations of S-K is associated with higher mortality, but a causal relationship remains to be established (Einhorn et al 2009, Nakhoul et al 2015).

ZS is a non-absorbed, inorganic crystalline compound that selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract after oral administration. Thereby excess potassium are removed from the body through faecal excretion and serum potassium is decreased.

A global clinical programme including more than 1800 patients with hyperkalaemia demonstrated the efficacy of ZS compared with placebo for correction of hyperkalaemia, with 88% of patients reaching normal S-K after 48 hours of treatment with ZS 10 g three times a day (tid). Maintenance of normokalaemia was also demonstrated, with lower mean S-K and increased number of normokalaemic days with ZS 5 g or 10 g once daily (qd) compared with placebo, and a lasting maintenance effect for up to 12 months. More details on the pharmacological properties, efficacy and safety of ZS are given in the Investigators' Brochure.

As ZS has been proven to be a safe and efficacious treatment for hyperkalaemia, a medication regimen containing ZS may allow more intensive RAASi therapy among patients otherwise not able to achieve treatment with RAASi at recommended doses due to hyperkalaemia. The underlying hypothesis is that more intense heart failure therapy, especially increased MRA use, will be safely facilitated by a treatment regimen containing ZS.

The current study is designed to evaluate the dose intensification of RAASi therapies on ZS or placebo. Intensified heart failure therapy is anticipated to reduce left ventricular wall stress, which will be assessed in this study using NT-pro-BNP and other endpoints.

2.3 Benefit/risk assessment

This study will recruit subjects who are mildly hyperkalemic or who are at high risk of developing hyperkalaemia, randomise such subjects to ZS or placebo, and subsequently attempt to up-titrate doses of RAASi therapies administered to target doses recommended in international heart failure guidelines. RAASi therapies have the potential to increase serum potassium and, hence hyperkalaemia is the major medical risk for subjects participating in the trial, especially as HF patients may be at an increased risk of hyperkalaemia induced arrhythmias. In addition, up-titration of RAASi therapies may result in hypotension and/or decreased renal function, as assessed by estimated glomerular filtration rate (eGFR). The following study design features were included to minimize the risk to subjects:

- Local labs will be used by sites to allow dose adjustments to occur rapidly at each visit by providing investigators with up-to date serum K and creatinine measurements.
- Subjects with local lab-K > 5.5 mmol/L before randomization are excluded to minimize the risk of subjects developing severe hyperkalaemia. Additionally, the provision to not up-titrate RAASi in subjects with a local lab S-K >5.0 mmol/L before levels start to decrease towards normal should also protect subjects against the risk of developing severe hyperkalaemia.
- Stopping rules are provided for subjects with local lab-K > 6.5 mmol/L or local lab-K <3.0 mmol/L as these subjects require immediate attention to the treatment of the potassium disorder.
- To minimize the potential risk of rebound hyperkalaemia when IP is discontinued, after IP discontinuation (Visit 8 or early discontinuation) the investigator should return to the original RAASi dose the patient was on prior to randomization and 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.
- Hypokalaemia has been reported in subjects treated with ZS. ZS titration down to 5 g every other day (qod), stopping rules for subjects with severe hypokalaemia, the use of local lab monitoring is included in this protocol to minimize the risk of hypokalaemia to recruited subjects.

- Oedema related events (grouped terms include preferred terms of oedema, oedema peripheral, generalized oedema, fluid overload, fluid retention, hypervolaemia, localised oedema, and peripheral swelling) have been reported by patients treated with ZS, in particular at higher doses. Patients with HF have a high likelihood of experiencing oedema. A physical examination will be performed, and the subject will be weighed at each visit to ensure any oedema development will be caught early and appropriately managed.

Prior studies with ZS have included patients with HF and on RAASi therapy. RAASi dose up-titration was allowed in study ZS-005 and did occur in some patients but was not required by the protocol. Earlier studies, including ZS-003, ZS-004 and ZS-004E did also include patients with HF, but RAASi up-titration was not allowed. The previous experience with ZS in patients with HF and treated with RAASi have not to date generated any safety signal precluding the use of ZS in patients with HF and on RAASi therapy.

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.

Participating subjects, irrespective of treatment allocation, may benefit from more intense monitoring and attention to their underlying condition. Patients randomised to receive ZS may benefit by being able to be treated with guideline-recommended target doses of RAASi, but due to the limited duration of this trial they are not expected to experience any significant clinical benefit by participating in this study. In the larger perspective the main potential benefit of conducting PRIORITIZE HF lies in the possibility to develop an improved treatment regimen for patients with moderate to severe heart failure with hyperkalaemia or at high risk of hyperkalaemia, and in the long term to improve outcomes for such patients.

Due to the limited potential risks to recruited subjects, the risk mitigation efforts included in this protocol to minimize risk to participants, and the potential long-term benefits of developing a treatment regimen for HF patients with or at high risk of hyperkalaemia, it is concluded that the study as proposed exposes recruited subjects to an acceptable risk considering the considerable potential long-term benefit of conducting the trial.

2.4 COVID-19 Pandemic Modifications

The study was terminated prematurely because of the COVID-19 pandemic, and study procedures were modified to ensure patient safety and trial integrity. The full details of these changes, in addition to their impact, can be found in Appendix I.

Specifically, as of April 01, 2020, all sites were asked to discontinue patients from the active treatment phase of the study. Sites were told to bring forward all patients who had not yet completed Visit 8 (End-of-Treatment visit) to conduct Visit 8 as soon as possible. At the end of Visit 8, sites were requested to withdraw the IP, and unblind each patient to the PI via the IVRS/ IWRS system. For patients on placebo, the patients should have been managed as deemed appropriate by the investigator. For the patients on Lokelma, patients should have been RAASi down-titrated to pre-randomization (or lowest) doses, and potassium should have

been checked at 48 hours and also 7 days post IP discontinuation. Visit 9, a safety follow-up visit 7 days after IP discontinuation, should have been conducted for all patients.

3. OBJECTIVES AND ENDPOINTS

Table 2 Study objectives

Primary Objective:	**Endpoint/Variable:**
To determine if there is a difference between ZS 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 Objectives:	**Endpoint/Variable:**
To evaluate the safety and tolerability of ZS 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 ZS 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 ZS 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 ZS 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 ZS 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 ZS and placebo in 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 is defined in the Statistical Analysis Plan.

To explore change of blood pressure in the ZS 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 ZS 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 ZS group compared with the placebo group.	Change in NYHA class from baseline.
To explore the effect of treatment with ZS 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 ZS	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).

4. STUDY DESIGN

4.1 Overall 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 (ZS) to intensify RAASi therapy in patients with heart failure, in particular through the initiation of MRA treatment, but also through up-titration of ACEi, ARB or ARNI therapy, without inducing clinically significant hyperkalemia. Eligible subjects will have chronic heart failure (NYHA II-IV) and be mildly hyperkalaemic (S-K: 5.1-5.5) and/or be at high risk of developing hyperkalaemia. Subjects will be randomised in a 1:1 ratio to receive ZS or placebo for 3 months while titrating RAASi therapies.

For an overview of the study design, see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

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

For details on the COVID-19 pandemic impact, see Appendix I.

4.2 Scientific rationale for study design

4.2.1 Rationale for patient population

Eligible subjects with HF but not receiving recommended target doses of RAASi therapies (MRA therapy and/or ACEi/ARB/ARNI therapy) with hyperkalaemia or at high risk to develop hyperkalaemia will be included in the study, as this is the population in which ZS is anticipated to be able to provide a benefit to patients.

Eligible HF subjects must have ejection fraction ≤ 40%, be assessed as NYHA functional class II-IV, and receive ACEi/ARB/ARNI therapy as per guidelines. Subjects are expected to be receiving a beta-blocker per standard of care guidelines, however patients in whom beta-blockers are contraindicated are eligible for inclusion.

Since MRAs are more often associated with hyperkalaemia that limits adequate dosing, it is important to demonstrate that ZS allows MRA introduction and up-titration. Therefore, patients treated with MRA at target doses at baseline are excluded. Instead, patients should be on either no MRA or a low dose MRA that was not increased specifically due to prior, documented hyperkalemia. Low dose is defined as less than or equal to spironolactone 12.5 mg QD (or 25 mg QOD) or equivalent for the patient to qualify.

The patient population will be enriched for subjects at risk of developing hyperkalaemia during up-titration of RAASi therapies by limiting inclusion to subjects with eGFR between 20 and 59 ml/min/1.73 m^2, and by requiring that subjects with eGFR ≥ 45 ml/min/1.73 m^2 should be either mildly hyperkaelemic or have a history of hyperkalaemia upon RAASi therapy even if normokaelemic at inclusion. This patient population would benefit the most from the use of ZS.

Patients with local lab-K >5.5 mmol/L are excluded since the up-titration of RAASi in such subjects may pose a risk in subjects receiving placebo.

Patients receiving agents binding potassium in the gastrointestinal tract, such as sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS) or patiromer, are excluded to avoid pharmacodynamic interactions with ZS.

4.2.2 Rationale for blinding and randomisation

The study employs blinding to minimize the risk for bias introduced by subjects, investigators and sponsor or sponsor representatives. Minimizing bias introduced by investigators and subjects is imperative as the primary endpoints of the trial can be influenced significantly by treatment choices made by the investigators in the trial and agreed with participating subjects.

Note that unblinding to the investigator, to facilitate patient management, was recommended to sites as part of the response to the COVID-19 pandemic (see Appendix I for details) once patients discontinued IP. Additionally, patients in the original protocol up through Amendment 3 were also unblinded after IP discontinuation, then managed by an unblinded investigator, for medication management. However, neither of these situations are expected to increase bias relating to the primary endpoint, as the unblinding occurred after collection of the primary endpoint data, and was not shared with the Sponsor. Randomisation is employed to minimize the risk for bias and produce comparable groups, and a 1:1 randomisation scheme was selected to maximize power and thereby minimize the number of subjects needed to be recruited.

4.2.3 Rationale for treatment groups

Patients randomised to receive ZS with local lab-K >5.0 mmol/L at the last assessment before randomization will be treated with ZS 10 g tid for 2 days followed by ZS 5 g qd, while normokalemic subjects will start ZS 5 g qd immediately after randomisation. The initial ZS 10 g tid treatment will ensure S-K is brought down to the normokalemic range rapidly, thereby increasing the chance RAASi up-titration can start at Visit 3 one week after randomisation. RAASi up-titration should not be initiated in subjects with local lab-K >5.0 mmol/L until there is evidence that S-K levels are decreasing toward normal, e.g. upon IP titration.

Patients randomised to placebo will continue their therapy as before randomisation, but may benefit from additional monitoring of their local lab-K and then subsequent up- or down-titration of their RAASi therapy.

Titration of ZS based on local lab-K values at each visit will be employed to ensure all subjects receive ZS at an individually optimized dose. Patients randomized to receive placebo will undergo mock titration to maintain the study blinding.

Placebo is used as comparator in PRIORITIZE HF as the primary efficacy endpoints could be affected by treating physicians knowing the treatment allocation of individual subjects, and as there is no other drug currently approved or widely used to allow up-titration of RAASi in patients at high risk of hyperkalaemia. Hence placebo is a necessary and appropriate comparator.

4.2.4 Rationale for objectives and endpoints

The purpose of PRIORITIZE HF is to assess if a treatment regimen containing ZS will allow RAASi therapies to be up-titrated to target doses in patients with heart failure and elevated serum potassium or at high risk of developing elevated serum potassium.

RAASi therapies are well known to improve cardiovascular and patient outcomes in HF, but are frequently underutilized in patients with HF due to concern for hyperkalaemia (Epstein et al 2016). This is particularly true for MRA use. The main objective of nothis study is to determine if there is a difference between ZS and placebo in RAASi treatment.

4.3 Justification for dose

ZS 10 g tid for 2 days hasbeen proven to be a tolerable and efficacious therapy to normalize S-K in hyperkalaemic patients (see data on the Correction Phase for studies ZS-003, ZS-004 and ZS-005 in the Investigator's Brochure).

ZS 5 g, 10 g, and 15 g qd has been proven to be tolerable and efficacious dose during longer term therapy in prior ZS studies (see data on the Maintenance Phase for studies ZS-004 and ZS-005 in the Investigator's Brochure)

The ZS / placebo dose will be titrated during this study based on a dose titration schedule further developed from the ZS dose titration schedule previously successfully used in ZS-005, see Section 6.6 for details.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject completing the study.

A subject is considered to have completed the study when he/she has completed visit 10.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

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

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol "enrolled" subjects are defined as those who signed informed consent and received an enrolment number. "Randomised" subjects are defined as those who undergo randomisation and received a randomisation number.

For procedures for the withdrawal of incorrectly randomized subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply, with the exception of inclusion criterion 3:

Informed consent

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Provision of a signed and dated, written informed consent form prior to any mandatory study-specific procedures, sampling, and analyses.
3. Provision of signed and dated written genetic informed consent prior to the collection of the samples for genetic analysis. Individuals refusing to provide informed consent for genetic testing may still be included in the study, but will not have to provide samples for genetic analysis.

The ICF process is described in Appendix A 3.

Age

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

Type of subject and disease characteristics

5. Individuals with established documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV), which has been present for at least 3 months.
6. Individuals with left ventricular ejection fraction ≤ 40% (any measurement made within the past 12 months using echocardiography, multiple gate acquisition scan, computer tomography scanning, magnetic resonance imaging or ventricular angiography is acceptable, provided no subsequent measurement above 40%).
7. Individuals receiving background standard of care for HFrEF and treated according to locally recognized guidelines with both drugs and devices, as appropriate. Therapy with ACEi/ARB/ARNI, MRA and beta-blocker should have been stable for ≥4 weeks prior to randomization. Subjects must be treated with an ACEi or an ARB or ARNI to be eligible. Subjects who are not being treated with beta-blockers because of a contraindication are eligible. Subjects should be 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. If patients are taking a low dose MRA, the rationale for the low dose must be the patient could not tolerate a higher dose due to documented hyperkalemia observed at higher doses.
8. Individuals with mild hyperkalaemia or at risk of developing hyperkalaemia during the study, as defined by meeting all of the criteria in any one of the 3 categories listed below:
    a. eGFR 20-44 ml/min/1.73m^2 by CKD-EPI and local lab-K 4.0-5.5 mmol/L inclusive, or
    b. eGFR 45-59 ml/min/1.73m^2 by CKD-EPI and local lab-K 5.1-5.5 mmol/L inclusive, or
    c. eGFR 45-59 ml/min/1.73m^2 by CKD-EPI and local lab-K 4.0-5.0 mmol/L inclusive and a documented history of S-K > 5.0 mmol/L due to RAASi.

Reproduction

9. Women of childbearing potential must have a negative pregnancy test during screening (before the first dose of IP) performed locally. Sexually active women of childbearing potential must be using a highly effective medically acceptable contraception method such as:

- combined hormonal contraception associated with inhibition of ovulation,
- progesterone only hormonal contraception, associated with inhibition of ovulation,
- intrauterine device (IUD),

- intrauterine hormone-releasing system (IUS),
- bilateral tubal occlusion,
- vasectomized partner, or
- sexual abstinence (true abstinence in line with the subjects preferred and usual lifestyle). Subjects practicing abstinence will agree to have a documented second acceptable method of birth control such as a combination of the following: (1) oral contraceptive, depo progesterone or intrauterine device; and (2) a barrier method (condom or diaphragm), should they become sexually active during the course of study participation).

Women who are surgically sterile or those who are postmenopausal for at least 2 years are not considered to be of childbearing potential.

Contraceptive methods must be practiced upon being randomized to the study and through 12 weeks after the last dose of study treatment. If a subject discontinues prematurely, the contraceptive method must be practiced for 12 weeks following the final administration of the study drug.

5.2 Exclusion criteria

Medical conditions

1. HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease.

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

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

4. Implantation of a Cardiac Resynchronization Therapy (CRT) device or Implantable Cardioverter Defibrillator (ICD) within 12 weeks prior to enrolment or intent to perform atrial fibrillation ablation or to implant a CRT device.

5. Previous cardiac transplantation or implantation of a ventricular assistance device (VAD) or similar device, or transplantation or implantation expected after randomization.

6. Symptomatic bradycardia or second (Mobitz type 2) or third-degree heart block without a pacemaker.

7. Symptomatic hypotension or systolic blood pressure (BP) <95 mmHg on 2 consecutive measurements.

8. Receiving dialysis or anticipated by the investigator to require dialysis therapy within 3 months.

9. Prior history of hypersensitivity to a RAASi drug, including but not limited to development of angioedema, icterus, hepatitis, or neutropenia or thrombocytopenia requiring treatment modification.

10. Addison's disease or other causes of hypoaldosteronism.

11. Known hypersensitivity to ZS.

12. Any condition outside the cardiovascular (CV) and renal disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgement.

13. Active malignancy requiring treatment.

Prior/concomitant therapy

14. MRA therapies that are mainly investigational and/or are not widely available as an oral dosing formulation (eg, canrenoate and finerenone) are excluded.

15. Treated with potassium binding resins such as sodium polystyrene sulfonate (SPS; e.g. Kayexalate®) or calcium polystyrene sulfonate (CPS; e.g. Resonium®) or the cation exchange polymer, patiromer sorbitex calcium (Veltassa®) within 7 days prior to the first dose of study drug.

16. Treated with potassium supplements within 7 days prior to randomization.

Prior/concurrent clinical study experience

17. Participation in another clinical study with ZS at any time or treatment with any investigational product (IP) during the last 3 months.

Other exclusions

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

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

20. Previous randomisation in the present study.

21. Subjects with a family history of long QT syndrome, presence of cardiac arrhythmias or conduction defects that require immediate treatment, or a QTc of ≥550 msec.

5.3 Lifestyle restrictions

No additional lifestyle restrictions are required by this study. Study sites are encouraged to instruct participants to adhere to any lifestyle restrictions they apply for similar patients not participating in a trial.

5.3.1 Meals and dietary restrictions

No additional dietary restrictions are required by this study. Study sites are encouraged to instruct participants to adhere to any dietary restrictions they apply for similar patients not participating in a trial.

5.3.2 Caffeine, alcohol, and tobacco

No general restrictions but see the Section 8.2.3 on restrictions prior to blood pressure measurement.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study and assigned enrolment number but are not subsequently randomly assigned randomization codes. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse event (AE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Patients that are rescreened should not be given a new enrolment number.

These subjects should have the reason for screen failure recorded in the electronic Case Report Form (eCRF).

6. STUDY TREATMENTS

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

6.1 Treatments administered

6.1.1 Investigational products

Table 3 Study Treatments

	Treatment 1	Treatment 2
Study treatment name:	Sodium Zirconium Cyclosilicate (ZS)	Placebo
Dosage formulation:	Powder for oral suspension in a 5 g sachet	Powder for oral suspension in a sachet
Route of administration	Oral use	Oral use
Dosing instructions:	A single dose consists of one to three sachets that should be suspended in 45 mL of water by the subject.	A single dose consisting of one to three sachets that should be suspended in 45 mL of water by the subject.
Packaging and labelling	Study treatment will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca

6.2 Preparation/handling/storage/accountability

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

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

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

Further guidance and information for the final disposition of unused study treatment will depend on local regulations in a given study country.

The randomized treatment phase will have a double-blind design. Patients will take by mouth assigned dose from the sachet(s) containing either ZS or placebo. The content of the sachet(s) is to be swirled down in 45ml water before ingestion. Sachets are enclosed in a carton with a tamper evident seal intended to be broken exclusively by subjects just before taking the study drug.

6.3 Measures to minimise bias: randomisation and blinding

Eligible subjects will be assigned a unique randomisation code and randomised to study treatment using an interactive voice response system or interactive web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS/IWRS and/or the log-in information and directions for the IVRS/IWRS will be provided to each site. Randomization will be stratified by country.

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

The IVRS/IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the subject at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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

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

6.4 Treatment compliance

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the Investigational medicinal products (IMP) from receipt by the study site until the destruction or return of all unused IMP. The Investigator(s) is responsible for ensuring that the subject has returned all unused IMP.

6.5 Concomitant therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Fixed-dose combination therapies (FDCs) will be recorded using the brand name for the FDC, except for FDCs where one of the components is a RAASi therapy listed in Table 5. FDCs containing a RAASi therapy component will instead be reported as a separate treatment for each FDC component on the concomitant medications Case Report Form (CRF) page to allow proper assessment of RAASi treatment intensity. An exception to this requirement is the administration of an ARNI; for that class of medication (see Table 5) it should be reported using the brand name as one entry.

Table 4 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it is allowed).
Drugs administered primarily to lower S-K (e.g. potassium binders). Diuretics administered to manage HF symptoms are allowed.	All treatments intended to lower S-K must be withheld during the treatment period, except as detailed in Section 6.5.3.
Potassium substitution or other drugs administered primarily to raise S-K (e.g. KCl)	All treatments intended to raise S-K must be withheld during the treatment period, except as detailed in Section 6.5.3.
Drugs with pH dependent absorption (see Section 6.5.4 for details)	Drugs with pH-dependent absorption should be administered at least 2 hours before or 2 hours after ZS to mitigate the risk of drug interactions.

6.5.1 RAASi treatment

RAASi treatments include two types: 1) ACEis, ARBs, or ARNIs, and 2) MRAs.

The titration of both types of RAASi treatments to the highest tolerable dose is the main objective of the trial, and as such should be given appropriate attention by investigators and study staff. Reasons for not increasing RAASi treatment while the patient is taking IP will be collected in the CRF.

General principles for titration of RAASi treatment:

- Up-titration of RAASi therapy should be done in the following order:
  1. Adding an MRA (if patient is not already on a low dose), THEN
  2. Titrating the MRA to the target or maximum tolerated dose, THEN

3. Increasing ACEi/ARB/ARNI to a target dose or a maximum tolerated dose if not already at target dose (Table 5).

- When MRA is initially added (if the patient is not already on low-dose MRA):
  - The patient must be seen 3 (+/-1) days later.
  - The typical starting dose for spironolactone is 25 mg QD. However, investigators may consider lower doses (eg, 25 mg QOD, 12.5 mg QD, or 12.5 mg QOD) if medically warranted. Similar adjustments may be considered for other MRAs (Table 5).
- At every study visit during the treatment period an attempt should be made to initiate or up-titrate the RAASi therapy administered. Patients who are at a target dose with one MRA and one ACEi/ARB/ARNI, or, in the opinion of the investigator, are already titrated to the maximum safe and tolerated RAASi treatment, should not be further up-titrated.
- Each up- or down-titration of RAASi therapy will require an additional study visit to be performed 7 (+/-2) days later, with the exception of MRA initiation that requires reassessment in 3 (+/-1) days later (see Schedule of Activities (SoA) for details). The investigator should always consider an earlier study visit if he or she has any concerns of subject safety (eg, in cases of hyperkalemia). If MRA initiation and IP and/or ACEi/ARB/ARNI titration occur at the same visit, requiring a dose change visit within 3 (+/-1) days and another within 7 (+/-2) days, only the earliest dose change visit should be performed.
- Evidence of poor RAASi tolerability may include, but is not limited to, local lab-K > 5.0 mmol/L, hypotension, clinically significant decline of eGFR (based on investigator judgement), and eGFR < 20 ml/min/1.73m^2. If a subject exhibits any of the above, the following should be considered:
  - Up-titration of RAASi therapies should not be performed until tolerability improves, e.g. S-K is decreasing towards normality, e-GFR is stabilizing and equal or above 20 ml/min/1.73m2
  - Down-titration of RAASi therapies may be considered based on investigator judgement
  - If local lab K >5.0 and $\leq$6.0 mmol/L, consideration should be given to first up-titrating IP (see Section 6.6 and Appendix F), then rechecking K within 7 days to determine if K is decreasing toward normokalemia, prior to down-titrating RAASi.
- After IP discontinuation, if subjects had RAASi medication increases or new medications added, the subjects should be switched back to the doses of RAASi therapy they were on prior to randomization. If subjects had RAASi medication down-titrated or stopped from their baseline during the study, they should be given the lowest RAASi medication doses. For any study visits following at least one week after drug discontinuation (eg, Visits 9 and 10 if the subjects discontinues at

Visit 8 per protocol), investigators should optimize RAASi medication based on their clinical judgement.

The following are recommendations for the investigator to consider, but not following these recommendations will not constitute a protocol deviation:

- As per HF treatment guidelines subjects should only receive one drug from the ACEi, ARB and ARNI classes.
- It is allowed to switch between ACEis/ARBs/ARNIs, e.g. if a subject experiences dose limiting cough.
- Switching between ACEis/ARBs/ARNIs is done by stopping the ACEi/ARB/ARNI and starting the new ACEi/ARB/ARNI on the subsequent day (when stopping ACEi) or the day thereafter (when stopping ARBs or ARNI).

Proposed starting doses, dose escalation steps, and target doses for RAASi treatments are displayed in Table 5.

Table 5 RAASi treatments

Drug Class:	Drug	Initial dose	Dose escalation	Target dose
ACEi	Benazepril	5-10mg qd	10, 20, 40	40mg qd
	Captopril	6.25mg tid	6.25, 12.5, 25, 50	50mg tid
	Cilazapril	0.5mg qd	0.5, 1, 2.5, 5	2.5-5mg qd
	Delapril	7.5mg bid	7.5, 15, 30	30mg bid
	Enalapril	2.5mg bid	2.5, 5, 10, 20	10-20mg bid
	Fosinopril	5-10mg qd	5, 10, 20, 40	40mg qd
	Moexipril	7.5mg qd	7.5, 15, 30	30mg qd
	Lisinopril	2.5-5mg qd	2.5, 5, 10, 20, 40	20-35/40mg qd
	Perindopril	2mg qd	2, 4, 8, 16	8-16mg qd
	Quinapril	5mg bid	5, 10, 20	20mg bid
	Ramipril	1.25-2.5mg qd	1.25, 2.5, 5, 10	10mg qd
	Trandolapril	1mg qd	1, 2, 4	4mg qd

Drug Class:	Drug	Initial dose	Dose escalation	Target dose
ARB	Azilsartan	40-80mg qd	40, 80	80mg qd
	Candesartan	4-8mg qd	4, 8, 16, 32	32mg qd
	Eprosartan	400-600mg qd	400, 600	600mg qd
	Irbesartan	75mg qd	75, 150, 300	300mg qd
	Losartan	25-50mg qd	25, 50, 100, 150	50-150mg qd
	Olmesartan	20mg qd	20, 40	40mg qd
	Telmisartan	40mg qd	40, 80	80mg qd
	Valsartan	20-40mg bid	20, 40, 80, 160	160mg bid
ARNI	Sacubitril/Valsartan	24/26mg bid	24/26, 49/51, 97/103	97/103mg bid
MRA	Spironolactone	25mg qd (consider lower if needed; 25 mg qod, 12.5 mg qd, or 12.5 mg qod)	50 mg qd (or, intermediate dose if starting <25 mg qd)	50 mg qd
	Eplerenone	25mg qd	25, 50	50mg qd
	Canrenone	25-50mg qd	25, 50, 100	50-100mg qd

Table adapted from: Ponikowski et al 2016, Yancy et al 2017, and spironolactone US package insert. Wherever a range is provided in the Target dose column the lower end of the range is considered the Target dose for purposes of the statistical analysis.

6.5.2 Other concomitant treatment

Any medication considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator, but must be recorded in the appropriate sections of the Case Report Form.

6.5.3 Rescue medication

Rescue medication for subjects presenting with local lab-K ≥6.0 mmol/L or local lab-K <3.0 mmol/L will not be provided. Instead, subjects developing local lab-K ≥6.0 mmol/L or local lab-K <3.0 mmol/L at any time during the study should be treated according to the investigator's medical judgement using standard of care and monitored more intensely until local lab-K has been confirmed to be between 3.5 and 5.5 mmol/L inclusive. RAASi

treatments may be down-titrated/discontinued and potassium binders, insulin and glucose, other potassium lowering drugs, or potassium supplements may be administered at the investigator's discretion and as medically appropriate. Additional study visits may occur at any time at the investigator's discretion to ensure safety and protocol adherence.

6.5.4 Drugs with pH-dependent absorption

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 treatment to mitigate the risk of drug interactions.

Drugs that should be taken 2 hours before or after study treatment to avoid a possible raised gastric pH drug interaction are listed in Table 6.

Table 6 Drugs with pH dependent absorption

Class of drug	Drugs
Anti-HIV drugs	Amprenavir, atazanavir, delavirdine, fosamprenavir, indinavir, ledipasvir, nelfinavir, raltegravir, rilpivirine, ritonavir, saquinavir
Antibiotics	Cefditoren, clarithromycin
Antiepileptics	Gabapentin, phenytoin
Antimycotics	Itraconazole, ketoconazole, posaconazole, Voriconazole
Bisphosphonates	Risedronic acid
Cardiac glycosides	Digoxin
Immunosuppressants	Methotrexate, mycophenolate mofetil, mycophenolic acid, tacrolimus
Intestinal anti-inflammatory agents	Mesalamine
Iron preparations	Iron salts
Tyrosine kinase inhibitors	Acalabrutinib, dasatinib, erlotinib, gefitinib, nilotinib, pazopanib

6.6 Dose modification

IP should be up- or down-titrated depending on the currently administered dose of IP and the local lab-K at every study visit. Each up- or down-titration of IP will require an additional study visit to be performed 7 (+/-2) days later (see Schedule of Activities (SoA) for details). See Appendix F for further information regarding the titration of IP.

If an IP titration and MRA initiation occur at the same visit, requiring a dose change visit within 3 (+/-1) days and another within 7 (+/-2) days, only the earliest dose change visit should be performed.

6.7 Treatment after end of study treatment

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 not be returned to their original dose and should be given the lowest RAASi doses at the end of randomized therapy.

For any study visits following at least one week after drug discontinuation (eg, Visits 9 and 10 if the subject discontinues at Visit 8 per protocol), investigators may optimize RAASi medication based on their clinical judgement. Further down-titrating or stopping RAASi therapies, or starting commercially available potassium lowering therapies, are acceptable options to manage subjects with hyperkalaemia or at high risk of developing clinically significant hyperkalaemia at the end of the trial after the final safety visit (Visit 10).

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

Please refer to Appendix I for specific procedures impacted by the COVID-19 pandemic. In summary, many patients were asked to discontinue the active treatment phase of the study due to COVID-19 and to conduct Visit 8 as soon as possible. At the end of Visit 8, PIs withdraw the IP, and unblinded patients via IVRS to enable medical management.

7.1 Discontinuation of study treatment

Every reasonable effort should be made to continue study treatment, and if study treatment must be discontinued, to keep the subject in the study. Note that discontinuation from study treatment is different from complete withdrawal from the study. After IP discontinuation (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 not be returned to their original dose and should be provided the lowest RAASi doses at the end of randomized therapy. For any study visits following at least one week after drug discontinuation (eg, Visits 9 and 10 if the subjects discontinue at Visit 8 per protocol), investigators may optimize RAASi medication based on their clinical judgement.

Subjects may be discontinued from the investigational product (IP) in the following situations.

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event precluding further therapy
- Severe non-compliance with the Clinical Study Protocol

- Deteriorating renal function resulting in the initiation of permanent scheduled dialysis.
- Local lab-K <3.0 mmol/l or local lab-K >6.5 mmol/l, as detailed in Appendix F. See also guidance in Section 6.5.3 on rescue medications.
- If an absolute QTc >550msec, or an increase in QTc interval > 60msec from baseline to more than 500msec is reached the subject should immediately receive appropriate medical attention and be discontinued from the study treatment. The QTcF (corrected QT interval by Fredericia algorithm) is recommended.

  All patients meeting the QTc>500ms criterion should have S-K assessed by local lab, collected within 1 hour of the collection of the ECG.
- Pregnancy (see Section 8.4.2).

7.1.1 Temporary discontinuation

Subjects temporarily discontinuing IP may continue in the study and may re-initiate IP treatment. During the temporary discontinuation, additional unscheduled visits should be performed as outlined for "Dose change" visits in the Schedule of Activities (SoA). The investigator must take particular care to ensure subject safety during temporary discontinuation of IP, as the subject may be at risk to develop hyperkalaemia, and additional visits or assessments are allowed at the investigator's discretion.

The investigator should handle the RAASi titration during a temporary discontinuation in the same way as during a permanent discontinuation. Specifically, after temporary IP 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 not be returned to their original dose and should be given the lowest dose of RAASi. If the patient restarts IP, then the investigator can re-optimize RAASi therapy as per protocol guidelines.

7.1.2 Procedures for discontinuation of study treatment

The investigator should instruct the subject to contact the site before or at the time if study treatment is stopped. A subject that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of the last intake of study treatment should be documented in the CRF. All study treatment should be returned by the subject at their next on-site study visit.

Following IP discontinuation, the study site and subject should continue to complete all visits as defined in the Schedule of Activities (SoA). The subject should continue attending subsequent study follow-up visits and data collection should continue. If the subject does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the subject, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject that agrees to the

modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study

7.2 Lost to follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at the end of the study.
- Data on unreachable subjects may be collected from third parties, e.g. the subject's treating physician, if the subject has provided consent for this on the informed consent form.

7.3 Withdrawal from the study

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

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

Data collection from third parties, e.g. the subject's treating physician, may continue if the subject has provided consent for this on the informed consent form, except for if the subject withdraws this consent.

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

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

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

7.4 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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, provide 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 Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) or local health authorities, the sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study specific procedures should only be performed after signed informed consent has been obtained.

Consented subjects will be assigned a unique enrolment number via IVRS/IWRS. The enrolment number will be used throughout the study and will not be used for any other participant.

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

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

Eligible subjects will be assigned a unique randomisation code and randomised to study treatment using an IVRS/IWRS.

The investigator will ensure that data are recorded on the electronic Case Report Forms (CRFs).

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 CRFs. A copy of the completed CRFs will be archived at the study site.

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

Adherence to the study design requirements, including those specified in the Schedule of Activities (SoA), is essential and required for study conduct.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required (assumed to be 5 x 'Dose Change' visits), should be approximately 250 ml. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Refer to Appendix I for all changes due to the COVID-19 pandemic.

8.1 Efficacy assessments

The primary efficacy outcome measurement is based on the RAASi treatment intensity achieved.

8.1.1 RAASi treatment intensity

RAASi treatment intensity will be estimated based on the data provided by investigators in the CRF. The CRF will capture all concomitant drugs administered, and the RAASi treatment intensity will be derived from the collected data. The target doses provided for each RAASi drug in Table 5 will be used to assess if the target dose has been achieved. Details will be provided in the Statistical analysis plan (SAP).

8.1.2 Potassium

Serum samples will be analysed locally using local lab to generate local lab-K for the purposes of study inclusion and monitoring. Samples drawn at the same time-points will be prepared and shipped to the Central Laboratory for analysis of S-K.

All serum samples should be examined and any hemolysed samples must be redrawn.

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

8.1.3 Patient reported outcomes (PROs)

PROs are an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating the effectiveness of treatments in clinical trials. The following

PROs will be administered in the study: PGIC and KCCQ (see Appendix H). Patients will be asked to complete the PROs at the visits as specified in the SoA.

8.1.3.1 Patient global impression of change (PGIC)

The PGIC question will be used to capture subjects overall change in HF symptoms since the start of the treatment.

8.1.3.2 Kansas City Cardiomyopathy Questionnaire (KCCQ)

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 Clinical Summary Score incorporates the symptom and physical limitations domains into a single score. Scores are transformed to a range of 0-100. Higher scores represent a better outcome.

8.1.3.3 Administration of PROs

Patients will complete the PRO assessments at the study site using a paper questionnaire. Each site must allocate the responsibility for the administration of the PROs to a specific individual and, if possible, assign a backup person to cover if that individual is absent.

All PRO assessments should be completed as follows:

- Patient must not receive help from relatives, friends, or site personnel to answer or clarify the PRO questionnaires in order to avoid bias. If a subject uses visual aids (eg, spectacles or contact lenses) for reading and does not have them at hand, the subject will be exempted from completing the PROs questionnaires on that visit.
- Before other study procedures are conducted at a given visit is recommended.
- Before being seen by the investigator.
- PRO questionnaires must be completed by the subject in private.
- The appointed site personnel should explain to subject the value and relevance of PRO assessments and inform them that these questions are being asked to find out, directly from subjects, how they feel. The appointed site personnel should also stress that the information is confidential.
- The appointed site personnel must show subjects how to complete the questionnaire in accordance with the instructions provided.
- The appointed site personnel should remind subjects that there are no right or wrong answers, and the subject should be given sufficient time to complete the questionnaire at his/her own speed.

If the subject is unable to read the questionnaire (eg, is blind or illiterate), the subject will be exempted from completing the PRO questionnaires and may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site personnel.

8.1.4 NYHA class

The definition of NYHA class is included in Appendix G. The investigator will evaluate this according to the Schedule of Activities (SoA) and assessment will be recorded in the CRF.

8.1.5 Urine analysis

First morning void spot urine will be collected at the time-points indicated in the Schedule of Activities (SoA). Urinary albumin and creatinine will be measured at the central laboratory and reported, and UACR will be calculated based on the measured urinary albumin and creatinine and reported.

Urine collection kits will be handed out at the visit before the visit when urine is to be collected to allow the subject to collect urine in the morning before the visit and on the morning the day before the visit. Hence two urine samples will be collected for each time-point. Collected urine should be stored in a fridge until the subject leaves home for the visit.

In the event that a subject forgets to collect one or both first morning voids the samples can instead be collected on the first one or two mornings following the visit, and delivered to the study site.

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

See Table 7 for the list of clinical safety laboratory tests to be performed and to the Schedule of Activities (SoA) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the Schedule of Activities (SoA).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed, dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

The routine clinical chemistry, haematology and urinalysis will be performed at a central laboratory, with the exception of K and creatinine measurements performed both locally using local lab and at the central lab at each visit, and pregnancy tests performed only locally. Samples for serum potassium and creatinine analysis using local labs should be collected according to sample collection and processing requirements for these parameters. Potassium and creatinine measured locally will be used for subject management and for study inclusion (potassium and creatinine), and will be reported in the CRF, but samples collected at the same time and analysed at the central laboratory will be used for the main statistical analyses.

Sites are encouraged to use local labs that can provide potassium and creatinine results as rapidly as possible. If the site can obtain the results in a reasonable time (as determined by the Investigator and the subject), the local labs can be drawn at the beginning of each visit, and then the patient medications titrated and/or IP dispensed before the patient leaves the clinic.

The maximum amount of time between local lab sample collection and obtainment of data results should be one day. If blood samples for local lab are taken at the study visit and the results are not known prior to the subject leaving the visit, the investigator may call the subjects or bring them back the following day for instructions regarding concomitant medication titration and IP dosing. Alternatively, if more feasible for the subject and Investigator, blood samples for the local lab may be collected one day before study procedure in cases when the local lab sample analysis time is expected to be longer than the duration of the subject's clinic visit.

At Visit 2 potassium and creatinine performed locally using local lab will be analysed before assessment against the inclusion criteria and randomization. It is recommended to perform the Visit 2 local lab assessment of creatinine and potassium before other Visit 2 assessments, with the exception of the KCCQ questionnaire, as the local lab assessment is likely to trigger the most screening failures.

Additional safety samples may be collected ('unscheduled') if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF. If additional safety analyses of potassium or creatinine (with or without subsequent calculation of eGFR), then local lab should be used to perform the analysis of the additional safety samples.

Estimated GFR (eGFR) will be calculated using the CKD-EPI (chronic kidney disease epidemiology collaboration equation) formula for each time-point when creatinine is analysed.

Table 7 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S-Creatinine
B-Leukocyte count	S-Bilirubin, total
B-Leukocyte differential count (absolute count)	S-Alkaline phosphatase (ALP)
B-Platelet count	S-Aspartate transaminase (AST)
	S-Alanine transaminase (ALT)
	S-Albumin
	S-C-reactive protein (CRP)
	S-Potassium
	S-Calcium, total
	S-Sodium
	S-Phosphorous
	S-Magnesium
	S-Bicarbonate
	S-Blood urea nitrogen (BUN)
	S-Creatine kinase (CK)

NB. In case a subject shows an AST **or** ALT ≥ 3 × upper limit of normal (ULN) together with total bilirubin ≥ 2 × ULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.2.2 Physical examinations

A complete physical examination will be performed at baseline as indicated in the Schedule of Activities (SoA) and will include an assessment of general appearance, respiratory system, cardiovascular system (including signs of fluid overload), abdomen, skin, head, and neck (including ears, eyes, nose and throat), lymph nodes, thyroid gland, musculo-skeletal system (including spine and extremities) and neurological system.

A targeted physical examination will be performed at the time-points indicated in the Schedule of Activities (SoA) and will include an assessment of general appearance, respiratory system, cardiovascular system (including signs of fluid overload), and abdomen.

Investigators should pay special attention to clinical signs related to previous serious illnesses (including HF, renal impairment, signs of fluid overload, and diabetes). New or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

Height will be assessed using locally available tools without the subject wearing shoes, and recorded in the CRF.

Weight will be assessed using the same scale, properly maintained and calibrated at each visit, and with the subject wearing a similar amount of clothes (e.g. underwear only or light indoor clothing only) at each visit.

8.2.3 Vital signs

Vital signs will be taken before blood collection for laboratory tests, and will consist of pulse and systolic and diastolic blood pressure measurements.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

Systolic and diastolic blood pressure will be measured 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. The use of aneroid manometers should be avoided. An 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 systolic blood pressure (SBP) differ by more than 5 mmHg, additional readings should be obtained.

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 subject 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 (preferably the dominant arm), by the same personnel, and with the same apparatus.

8.2.4 Electrocardiograms

12-lead ECG will be obtained at the time-points indicated in the SoA (see Section 1.1) using a digital ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT (using QTcF) intervals. For patients with pacemakers and ECGs demonstrating paced rhythms, there should be a manual reading of PR, QRS and QT to increase accuracy of the assessment in this population, while the automatically read values should be reported for non-paced ECGs.

8.3 Collection of adverse events

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

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

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

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

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

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

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

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

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit?*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known, and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values or 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.

8.3.8 Hy's law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Potential Hy's Law.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the 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 Electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study subject has received any study drug

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel 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 provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.3 Overdose

ZS has been given to subjects at doses of up to 30 g per day for 1 to 3 days and up to 15 g per day for 11 months.

PRIORITIZE-HF requires a 48-hour "correction phase" with ZS 10g TID (only in patients with local lab serum-K >5.0 mmol/L), followed by a "maintenance phase" for all patients with doses ranging from 5g QOD to 15g QD. For this study, overdose is defined as any of the following:

- During the initial 2-day correction phase (applicable only for patients with pre-randomization local lab serum-K >5.0 mmol/L), any ZS dose greater than 30g within one day, or continuation of the correction dose (10g TID) for more than 72 hours
- During the maintenance period for all patients, a dose higher than 15g per day will be considered an overdose

AstraZeneca does not recommend any specific treatment for an overdose. Monitoring and symptomatic therapy, potentially including potassium substitution therapy to treat any hypokalaemia, may be considered by the investigator.

- 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 an AstraZeneca study drug occurs during 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 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs during 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 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

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

8.5 Pharmacokinetics (PK)

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

Approximately 6 ml of blood sample for deoxyribonucleic acid (DNA) isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA

8.8 Biomarkers

Biomarkers NT-pro-BNP and high sensitivity troponin I will be tested in plasma/serum to evaluate how they are affected by the addition of ZS.

In addition, samples will be collected and analysis may be performed on biomarkers thought to play a role in HF, chronic kidney disease, or potassium homeostasis to evaluate their association with observed clinical responses to ZS or the effect of ZS on the biomarkers.

Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to ZS, HF, chronic kidney disease, hyperkalaemia, and/or other diseases.

8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Medical Resource Utilization and Health Economics

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

8.10 Demography and medical history

Demographic parameters to be collected from subjects include sex, date of birth, race, and ethnic group.

Medical history parameters to be collected include relevant medical and surgical history. In addition, prior dialysis therapy will be collected.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The primary objective is to determine if there is a difference between ZS and placebo in RAAS blockade treatment.

The null hypothesis is that there is no difference between treatments in the distribution of proportion of patients in the RAAS blockade treatment categories, and the alternative hypothesis is that there is a difference. The hypothesis will be tested at a significance level of 5% using a chi-square test for homogeneity.

9.2 Sample size determination

The study will employ a 1:1 randomization scheme. A sample size of 280 subjects will allow for the 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.

9.3 Populations for analyses

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

Analysis set	Description
Enrolled	All subjects who sign the ICF.
Full analysis set	All randomised subjects.
Safety analysis set	All subjects randomly assigned to Study treatment and who take at least 1 dose of IMP.

9.4 Statistical analyses

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. A comprehensive statistical analysis plan describes the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary endpoint. Any deviations from this plan will be reported in the clinical study report.

For analyses involving potassium values, the central laboratory S-K will be used primarily.

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

9.4.1 Efficacy analyses

All efficacy analyses will be based on the Full analysis set including all randomised subjects. Subjects will be analyzed according to their randomized study medication.

9.4.1.1 Primary efficacy variable

The primary outcome measure is the proportions 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.

The RAAS blockade dose used in the primary variable will be the dose the patient is on the day before visit 8 (i.e. before any potential RAAS blockade titration/change based on unblinded information is made on visit 8).

Missing RAASi dose data at 3 months will be partially imputed for the derivation of the primary variable. A detailed description of the imputation algorithm can be found in the Statistical Analysis Plan.

The hypothesis of a treatment difference (ZS vs placebo) in the distribution of RAAS blockade treatment will be tested at a significance level of 5% using a chi-square test for homogeneity. P-value will be presented.

Sensitivity analysis of primary analysis

Since imputed values are included in the primary analysis, sensitivity analyses of the primary analysis aimed at evaluating the impact of missing / imputed data will also be performed. All sensitivity analyses will be described in detail in the Statistical Analysis Plan.The consistency of potential effect of SZC across pre-defined sub-groups will also be evaluated as specified in the SAP.

9.4.2 Safety analyses

The safety analysis set will be used for all safety analyses. Erroneously treated subjects (eg. those randomized to ZS 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 ZS and placebo will be accounted for in the randomized treatment group.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized for the treatment period. Number of subjects with events and percentages will be tabulated 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.

Adverse events occurring prior to randomization and during the follow-up period will be presented in listings.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to the most extreme value during treatment) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable lab abnormalities will be summarized.

Proportion of subjects with S-K < 3.5 mmol/L and <3.0 mmol/L and S-K >5.5 mmol/L and >6.0 mmol/L will be presented.

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.

ECG intervals will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable ECG abnormalities will be summarized.

9.4.3 Other analyses

Exploratory objectives will be presented using summary statistics. Ninety-five percent confidence intervals may be presented as measures of precision.

Further details on exploratory outcome measures (e.g. definition of *i*) RAASi dose increase for subjects who switch RAASi during treatment period, *ii*) equipotent MRA doses and *iii*) dose intensity score) are described in the SAP.

9.4.4 Methods for multiplicity control

Not applicable

9.5 Interim analyses

There are no interim analyses planned in this study.

9.5.1 Data Monitoring Committee (DMC)

An independent data monitoring committee (also called a Safety Review Committee) that is independent of the sponsor will be utilized for this study.

Appendix A 5 provides more details on the rationale for and the remit of the committee.

10. REFERENCES

Ambrosy et al 2014
Ambrosy AP, Gheorghiade M, Chioncel O, Mentz R J, Butler J. Global perspectives in hospitalised heart failure: regional and ethnic variation in patient characteristics, management and outcomes. J Am Coll Cardiol 2014; 63:1123-33.

Braunwald 2015
Braunwald E. The war against heart failure: the Lancet lecture. Lancet 2015; 385:812-24.

Cook et al 2014
Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014; 171:368-378.

Einhorn et al 2009
Citation. Lisa M. Einhorn, Min Zhan, Van Doren Hsu, Lori D. Walker, Maureen F. Moen, Stephen L. Seliger, Matthew R. Weir, Jeffrey C. Fink. The Frequency of Hyperkalemia and Its Significance in Chronic Kidney Disease. Arch Intern Med. 2009;169(12):1156–1162.

Epstein et al 2016
Epstein M, Alvarez PJ, Reaven NL, Funk SE, McGaughey KJ, Brenner MS, Benton W, Golestaneh L. Evaluation of clinical outcomes and costs based on prescribed dose level of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2016 Aug;22(11 Suppl):s311-s324.

Fleet et al 2012
Fleet JL, Shariff SZ, Gandhi S, Weir MA, Jain AK, Garg AX. Validity of the International Classification of Diseases 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. BMJ Open. 2012;2: e002011.

Green et al 2000
Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure for Heart Failure. J Am Coll Cardiol. 2000 Apr; 35(5):1245-55.

Henneman et al 2016
Henneman A, Guirguis E, Grace Y, Patel D, Shah B. Emerging therapies for the management of chronic hyperkalemia in the ambulatory care setting. Am J Health Syst Pharm. 2016 Jan 15;73(2):33-44.

Kovesdy 2015
Kovesdy CP. Management of Hyperkalemia: An Update for the Internist. Am J Med. 2015 Dec;128(12):1281-7.

Nakhoul et al 2015
Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV Jr, Navaneethan SD. Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease. Am J Nephrol. 2015;41(6):456-63.

Okumura et al 2016
Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; PARADIGM-HF Investigators and Committees*. Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). Circulation. 2016 Jun 7;133(23):2254-62.

Ponikowski et al 2016
Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975.

Spertus et al 2005
Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS; Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J. 2005 Oct;150(4):707-15.

Vasudevan et al 2017
Vasudevan A, Jazi HH, Won JI, Ball T, Patankar GR, Sarmast SA, Shin HJ, McCullough PA. Proc (Bayl Univ Med Cent). 2017 Apr; 30(2):139-142.

Yancy et al 2017
Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Aug;23(8):628-651.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

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

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

A 2 Financial disclosure

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

A 3 Informed consent process

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

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

If a subject declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the subject and he/she will not be excluded from other aspects of the study.

If a subject partner becomes pregnant during the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Subjects" and provide information about the pregnancy accordingly.

Subjects who are rescreened are required to sign a new ICF.

A 4 Data protection

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

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

An Executive Committee consisting of members independent of AstraZeneca has been established for the ZS development program in heart failure. See the Executive Committee

member contracts and/or charter for details. The Executive Committee designed significant aspects of this study protocol.

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

A data monitoring committee will be established to review emerging safety data at pre-defined intervals. The committee will include member(s) independent of the sponsor. See the independent data monitoring committee Charter for details on the scope and membership. The independent data monitoring committee may request unblinded data if needed to assess any emerging safety concerns. The independent data monitoring committee can recommend the study to be amended if necessary for the protection of the subjects participating in the trial.

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

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

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support the publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 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.

B 2 Definitions of serious adverse event

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

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

B 3 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).

B 4 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.

B 5 Important medical event or medical treatment

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

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

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

B 6 Intensity rating scale:

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

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

B 7 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 an 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.

B 8 Medication Error

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

A medication error is not a lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

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

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

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

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

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

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological sample(s) is an optional part of the study, then the subject may continue in the study.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the subject´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported either in the clinical study report (CSR) or as an addendum, or separately in a scientific report or publication.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be stored for a maximum of 15 years from the date of the last subject's last visit, after which they will be destroyed.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and** provide informed consent for the genetic sampling and analyses.

Exclusion criteria
Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:
Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood sample for genetic research will be obtained from the subjects at Visit 2 randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

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

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

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

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

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size
The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.
For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN

- TBL ≥ 2 × ULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.

- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the

outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Appendix F IP (ZS or placebo) dose titration

Patients with local lab-K >5.0 mmol/L at the last assessment before randomization will be treated with IP 10 g tid for 2 days followed by IP 5 g qd, while normokalemic subjects will start IP 5 g qd immediately after randomisation.

Table 8 IP Dose adjustment table

Current dose	Local lab-K (mmol/L)	Dose Adjustment
5 g Every Other Day (qod)	<3.0	Discontinue dosing
	3.0 – 3.9	No change[1]
	4.0 – 5.0	No change
	5.1 – 6.5	5 g qd
	> 6.5	Discontinue dosing
5 g Once Daily (qd)	< 3.0	Discontinue dosing
	3.0 – 3.4	5 g qod[1]
	3.5 – 3.9	No change on first occasion[1, 2]
	4.0 – 5.0	No change
	5.1 – 6.5	10 g qd
	> 6.5	Discontinue dosing
10 g qd	< 3.0	Discontinue dosing
	3.0 – 3.4	5 g qd[1]
	3.5 – 3.9	No change on first occasion[1, 2]
	4.0 – 5.0	No change
	5.1 – 6.5	15 g qd
	> 6.5	Discontinue dosing

Current dose	Local lab-K (mmol/L)	Dose Adjustment
15 g qd	< 3.0	Discontinue dosing
	3.0 – 3.4	10 g qd[1]
	3.5 – 3.9	No change on first occasion[1, 2]
	4.0 – 5.0	No change
	5.1 – 6.5	No change
	> 6.5	Discontinue dosing

[1] Increasing RAASi therapy should be considered at every visit as detailed in Section 6.5.1. However, for subjects exhibiting local lab-K < 4.0 mmol/L it is particularly important to attempt to increase the RAASi therapy administered.
[2] The ZS dose should not be changed at the first visit when local lab-K is found to be between 3.5 and 3.9 mmol/L. When local lab-K is between 3.5 and 3.9 mmol/L on the second consecutive visit the dose of ZS should be reduced to the dose listed for local lab-K 3.0 - 3.4 mmol/L.

Appendix G New York Heart Association (NYHA) Functional Classification

NYHA Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix H Patient Reported Outcome (PRO) questionnaires

H 1 Patient Global Impression of Change (PGIC) for Heart Failure Symptoms

Patient Global Impression of Change for Heart Failure Symptoms

Overall, how would you rate the change in your heart failure symptoms since starting this study?

☐ Much better

☐ Moderately better

☐ A little better

☐ About the same

☐ A little worse

☐ Moderately worse

☐ Much worse

H 2 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your heart failure and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue, or ankle swelling) changed?
   My symptoms of heart failure have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the <u>past 2 weeks</u>, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the <u>past 2 weeks</u>, how much has swelling in your feet, ankles or legs bothered you? It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all Bothersome	I've had no swelling
☐	☐	☐	☐	☐	☐

5. Over the <u>past 2 weeks</u>, on average, how many times has fatigue limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the <u>past 2 weeks</u>, how much has your fatigue bothered you? It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the <u>past 2 weeks,</u> how much has your shortness of breath bothered you?
It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
□	□	□	□	□	□

9. Over the <u>past 2 weeks,</u> on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
□	□	□	□	□

10. Heart failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
□	□	□	□	□

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
□	□	□	□	□

12. Over the <u>past 2 weeks</u>, how much has your heart failure limited you enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
□	□	□	□	□

13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
□	□	□	□	□

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way
□	□	□	□	□

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks?

Place an **X** in one box on each line

Activity	Severely Limited	Limited quite a bit	Moderately Limited	Slightly Limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	□	□	□	□	□	□
Working or doing household chores	□	□	□	□	□	□
Visiting family or friends out of your home	□	□	□	□	□	□
Intimate relationship with loved ones	□	□	□	□	□	□

Appendix I COVID-19 Pandemic – Study Management Plan

On 11 March 2020, the World Health Organization characterized the coronavirus disease, COVID-19, as a pandemic, and on 17 March 2020 the Sponsor decided to stop enrolment of new patients into the PRIORITIZE HF trial.

The Executive Committee, National Lead Investigators, and Sponsor thoroughly assessed the risk/benefit of the study, along with the rapidly evolving pandemic situation, in the 2 weeks following the enrolment stop. This study was unique in that vulnerable patients were not simply given investigational product (IP), but also had RAASi medications actively titrated during the trial, which necessitated frequent potassium monitoring and clinic visits that were deemed imprudent to continue during a world pandemic.

On 01 April 2020, the PRIORITIZE HF Executive Committee and Sponsor communicated the following urgent actions to all study sites globally:

- Bring forward ALL patients to conduct Visit 8 (End-of-Treatment visit) as soon as possible.
    - Complete Visit 8, following the protocol procedures described under this visit. Site or home visits can be considered, as permitted in your country, but must include a laboratory test for potassium. It is preferable to use your local laboratory per protocol, and also collect the V8 central laboratory samples. If that is not possible, please consider obtaining potassium results via another local commercial laboratory, iSTAT, or another point of care device, as available.
    - If the patient is found at Visit 8 (or when visit 8 is being arranged) to require medical attention outside the trial protocol, then a hospital/clinic visit should be organized according to the local arrangements currently in place.
    - At the end of V8, withdraw the IP, and unblind each patient via IVRS/ IWRS.
        - For patients on placebo, manage the patient as deemed appropriate by the investigator. If RAASi medication was up-titrated during the trial, patient management might entail reduction of RAASi and continued potassium monitoring. For patients that did not have up-titration of RAASi, follow-up may be less intense.
        - For patients on sodium zirconium cyclosilicate (Lokelma), down-titrate RAASi to pre-randomization (or lowest) doses, check potassium at 48 hours and also 7 days post IP discontinuation.
- Visit 9, a safety follow-up visit 7 days after IP discontinuation, should be conducted for all patients.

  - Phone or other remote visits may be considered most appropriate unless there is a strong clinical rationale to see the patient in person.
  - If possible, potassium should be measured per guidance in prior section (essential for patients who had been on sodium zirconium cyclosilicate (Lokelma) and/or who had RAASi changes at visit 8).

- Visit 10, a protocol specified follow-up visit one month after IP discontinuation, can also be performed remotely, or, in person if considered safe to do so for the patient and site, does not place undue burden on your healthcare system or go against any local regulations for non-urgent care during the pandemic.

If the above instructions cannot be followed, for instance if potassium cannot be measured in any way because access to labs is severely limited, contact Sponsor immediately to discuss the situation and the possibility to continue open-label Lokelma treatment pending the availability of a laboratory service.

Thus, a summary of the urgent changes required due to COVID-19 primarily included:

- A stop to enrolment on 17 March 2020
- Ending treatment early for all patients in the treatment phase as of 01 April 2020
  - Skipping all pre-planned visits between patients' current visit and V8
  - Unblinding these patients to facilitate medical management and potentially reduce clinic and lab visits
  - Adding a 48-hour K^+ measurement for those on active treatment, and suggesting more flexible K^+ monitoring for placebo patients based on their condition and/or whether RAASi medications were modified during the study

Benefit-Risk Assessment

AstraZeneca's primary goal was to minimize the risk of COVID-19 infection in the vulnerable high-risk study population that required multiple study visits, to protect safety and well-being of our study participants, sites personnel\, and colleagues, and to reduce the work load pressure on the health care system.

This study is unique in that vulnerable patients are not simply given investigational product (IP), but also have RAASi medications actively titrated during the trial, which necessitates frequent potassium monitoring and clinic visits. Considering the cardiovascular risk in combination with the age of the patients, and to maintain the risk-benefit balance, AstraZeneca concluded it was in the best interest to:

- Stop the enrolment and randomization of new patients
- Withdraw IP in ongoing patients. Investigators to be unblinded via IVRS/ IWRS to facilitate the management of the patients and reduce the need to visit a laboratory for potassium checks

- Allow follow-up visits 9 and 10 to be done as remote visits

Appendix J Abbreviations

Abbreviation or special term	Explanation
ACCF	American College of Cardiology Foundation
ACEi	Angiotensin Converting Enzyme Inhibitors
AE	Adverse Event
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
Anti-HIV	Anti-Human Immunodeficiency Virus
ARB	Angiotensin Receptor Blockers
ARNI	Angiotensin Receptor Blocker / Neprolysin Inhibitors
AST	Aspartate Transaminase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Grafting
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Novel disease caused by the coronavirus called SARS-CoV-2; declared a pandemic by World Health Organization on 11Mar2020
CPS	Calcium Polystyrene Sulfonate
CRF	Case Report Form (electronic/paper)
CRP	C-reactive Protein
CRT	Cardiac Resynchronization Therapy
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
DAE	Discontinuation of Investigational Product due to Adverse Event
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECGs	Electrocardiograms
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FDCs	Fixed Dose Combination Therapies
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
HL	Hy's Law
IATA	International Airline Transportation Association
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
MRA	Mineralocorticoid Receptor Antagonist

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NT-pro-BNP	N-terminal pro b-type Natriuretic Peptide
NYHA	New York Heart Association
PBO	Placebo
PCI	Percutaneous Coronary Intervention
PGIC	Patient Global Impression of Change
PHL	Potential Hy's law
PK	Pharmacokinetics
PREGREP	Pregnancy Report
PREGOUT	Pregnancy Outcome
PRO	Patient Reported Outcome
qd	Once a Day
qod	Every Other Day
QTcF	Corrected QT interval by Fredericia
RAASi	Renin Angiotensin Aldosterone System Inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
S-K	Serum Potassium
SoA	Schedule of Activities
SPS	Sodium Polystyrene Sulfonate
TBL	Total Bilirubin
TIA	Transient Ischemic Attack
tid	Three Times a Day
UACR	Urinary Albumin to Creatinine Ratio
ULN	Upper Limit of Normal
VAD	Ventricular Assistance Device
ZS	Sodium Zirconium Cyclosilicate (can also be abbreviated SZC in other documents)

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