

Cover Page for SAP

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NCT number	NCT05350969
Sponsor trial ID:	CDR132L-P2-01
Official title of study:	Phase 2, Multicenter, Randomized, Parallel, 3-arm, Placebo-controlled Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (HF-REVERT)
Document date*	11-October-2024

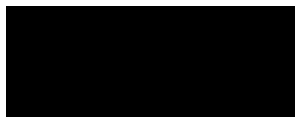
*Document date refers to the date on which the document was most recently updated.

Note: The date mentioned in the header (17 September 2025) from page 2 onwards is the finalization date of CSR and not of any update of the SAP.

Appendix 16.1.9 Documentation of Statistical Methods

[Statistical_Analysis_Plan_v2.0_11 October 2024](#)

*Redacted statistical analysis plan
includes redaction of personal identifiable and company
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Statistical Analysis Plan

Cardior Pharmaceuticals GmbH / Protocol: CDR132L-P2-01
() Project # QZA91424

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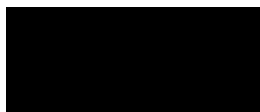
**Phase 2, Multicenter, Randomized, Parallel, 3-arm, Placebo-controlled Study to
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Statistical Analysis Plan

Version 2.0

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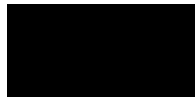
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Cardior Pharmaceuticals GmbH
Hollerithallee 20
30419 Hannover · Germany

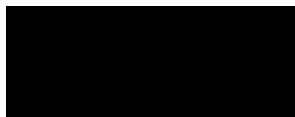
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Statistical Analysis Plan

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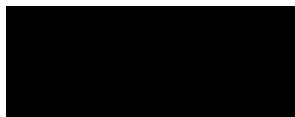
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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index
CI	Confidence Interval
CM	Concomitant Medication
COVID-19	Coronavirus disease 2019
ECHO	Echocardiography
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
GDMT	Guideline-Directed Medical Therapy
HDU	High-Dependency Care Units
HF	Heart Failure
ICU	Intensive Care Unit
ITT	Intent-to-treat
IV	Intravenous
IVRS/IWRS/IXRS	Interactive Voice/Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left atrial volume index
LOCF	Last Observation Carried Forward
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVESVI	Left ventricular end-systolic volume index
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
miR-132	MicroRNA-132
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
NSTEMI	Non ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro B-type natriuretic peptide
CCI	
PK	Pharmacokinetics



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PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOC	System Organ Class
STEMI	ST-segment elevation myocardial infarction
TEAE	Treatment Emergent AE(s)
WHO-DD	World Health Organization Drug Dictionary

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I. Introduction

A. Background

Current state-of-the-art Heart Failure (HF) pharmacotherapy is largely focused on symptomatic management. The recommended guideline-directed medical therapy (GDMT) includes diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone antagonists, angiotensin receptor neprilysin inhibitors, and ivabradine. Mechanical circulatory support and heart transplant is reserved for the treatment of patients with severe HF with reduced ejection fraction (EF) who have failed GDMT. Novel, efficient, disease-halting therapeutics that reduce mortality and hospitalization are urgently needed to offer curative hope for these patients. CDR132L is a unique miRNA-based next generation drug in HF, with the potential to improve patient care and thereby reduce the financial burden of HF care.

Several completed pre-clinical studies and the completed first-in-human (FIH) study assessing the pharmacokinetics (PK), pharmacodynamics (PD), pharmacology, safety pharmacology, and toxicological profile of CDR132L have demonstrated that the safety profile is adequate to progress with clinical development.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on Study Protocol Amendment 3.1 dated 16 May 2023.

Version	Approval Date	Salient Changes, if any*
Protocol	07 December 2021	n/a
Amendment 1	15 July 2022	n/a
Amendment 2_Greek	03 November 2022	n/a
Amendment 2_UK	03 November 2022	n/a
Amendment 3	30 March 2023	n/a
Amendment 3.1	16 May 2023	n/a

* Changes expected to require accommodation in analysis plan.

This SAP will govern the analysis of data from this study. The plan may be modified until first database lock and unblinding for the 6-month

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primary efficacy and safety analyses. Any amendments to the SAP will be documented, with final amendments completed before unblinding of the data for the primary analysis. Any deviations from the analysis plan after unblinding of the data for the primary analysis will be documented as such in the study report. A second database lock will be performed once the last patient has completed last visit (Day 360/Month 12) and data cleaning is complete. The clinical study report will be written following the completion of the study (Day 360/Month 12).

C. Changes to Planned Analyses from Protocol

The following changes from the protocol planned analyses and their rationale are noted in this plan:

- A modified Intent-to-Treat (mITT) analysis set has been defined to include all randomized subjects who receive at least 1 dose of study drug (CDR132L or placebo).
Rationale:
For analysis purposes, the mITT is added in the SAP.
- The analysis of the efficacy outcome measure will be performed using the mITT population.
Rationale:
From a medical perspective, it makes more sense to include subjects in the primary collective who received the study drug in this early phase trial, especially taking the small patient numbers into consideration.
- Additional test processes are added when the primary endpoints are successful. Details can be seen in [Section D.J. Multiple Comparisons](#).
Rational:
Additional tests are added because we want to get the most out of the study in terms of understanding the different elements of efficacy and connected endpoints to finally generate the right hypotheses for the upcoming clinical trials.

II. Protocol Objectives

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A. Primary Objective

To assess the efficacy of 2 dose levels (5 and 10 mg/kg) of CDR132L compared with placebo administered in 3 single IV doses given 28-days apart in subjects with reduced Left Ventricular Ejection Fraction (LVEF) $\leq 45\%$ after Myocardial Infarction (MI) (STEMI or NSTEMI) as add-on therapy to Standard of Care treatment.

B. Secondary Objectives

Confirmatory secondary objectives:

- To assess the efficacy of the pooled dose levels (5 and 10 mg/kg) of CDR132L compared with placebo in LVEF (%) at month 6.
- To assess the efficacy of the pooled dose levels (5 and 10 mg/kg) of CDR132L compared with placebo in NT-proBNP (pg/mL) (on a logarithmic scale) at month 6.
- To assess the efficacy of the pooled dose levels (5 and 10 mg/kg) of CDR132L compared with placebo in global longitudinal strain at month 6.
- To assess the efficacy of the pooled dose levels (5 and 10 mg/kg) of CDR132L compared with placebo in Overall Summary score in KCCQ at month 6.

Supportive secondary objectives:

- To assess the safety of 2 dose levels (5 and 10 mg/kg) of CDR132L compared with placebo
- To assess the effects of CDR132L compared with placebo on cardiac function
- To assess the effects of CDR132L compared with placebo on efficacy-related biomarkers
- To assess the effects of CDR132L compared with placebo on subject well-being

C. Exploratory Objectives

- CCI
-
-

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III. Study Endpoints

A. Primary Endpoint

Percent change from baseline (screening to occur at least 3 days (up to 14 days) after MI diagnosis as measured by Echocardiography (ECHO) [central laboratory]) in Left Ventricular End-systolic Volume Index (LVESVI) at Month 6.

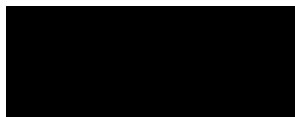
B. Secondary Endpoints

Confirmatory secondary endpoints:

- Absolute change from baseline in LVEF (%) at Month 6 with pooled dose levels (5 and 10 mg/kg).
- Absolute change from baseline in N-terminal pro B-type natriuretic peptide (NT-proBNP pg/mL) at Month 6 with pooled dose levels (5 and 10 mg/kg).
- Absolute change from baseline in global longitudinal strain (%) at Month 6 (absolute) with pooled dose levels (5 and 10 mg/kg).
- Absolute change from baseline in Overall Summary score in KCCQ at Month 6 (absolute) with pooled dose levels (5 and 10 mg/kg).

Supportive secondary endpoints:

- Change from baseline in LVEF (%) (absolute/relative) at Months 3, 6, and 12
- Change from baseline in absolute/relative values over time for the NT-proBNP (pg/mL) at Days 2 to 5, Months 1, 2, 3, 6, and 12.
- Change from baseline in LVESVI at Month 3 (absolute/relative), Month 6 (absolute), and Month 12 (absolute/relative)
- Frequency and nature of adverse events during the course of the trial, and abnormalities in clinical laboratory assessments, vital signs, physical examination, electrocardiograms (ECGs), and urinalysis at Months 3, 6, and 12



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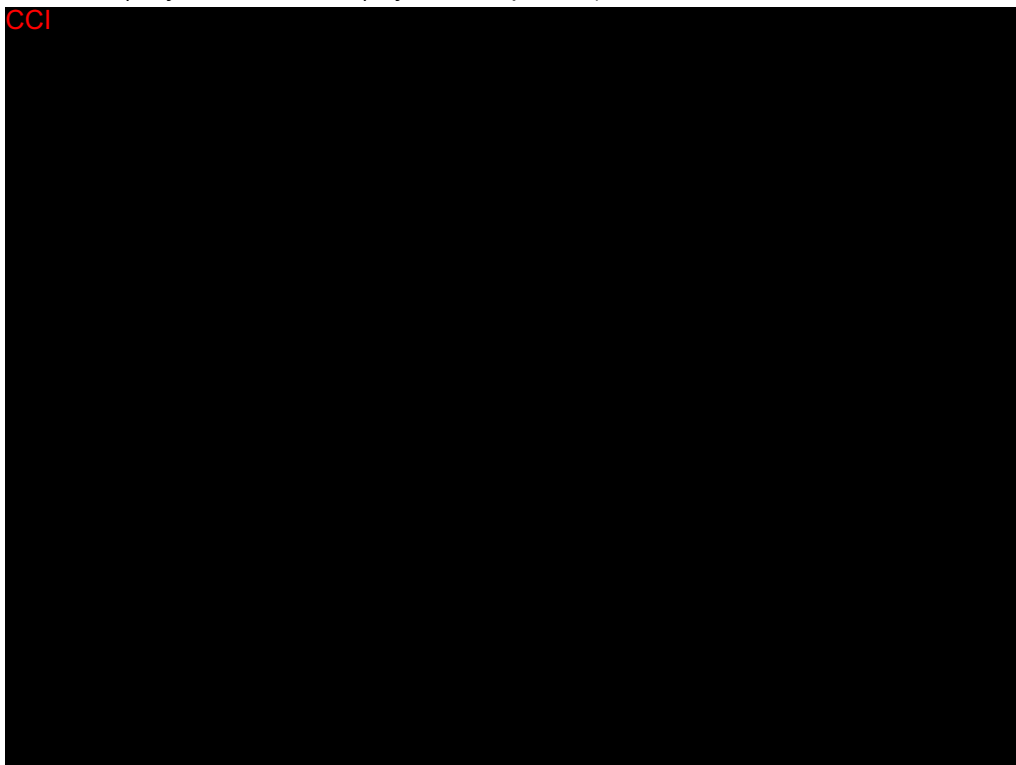
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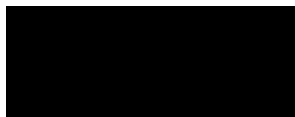
- Change from baseline in absolute/relative Troponin T (ng/L) at Months 3, 6, and 12
- Well-being as evaluated by change from baseline at Months 6 and 12 in the following parameters:
 - Mean Kansas City Cardiomyopathy Questionnaire (KCCQ - overall summary score) score and mean scores of subdomains (symptom burden, physical limitation, and quality of life)

C. Exploratory Endpoints

The following endpoints will be analyzed in an exploratory manner. However, other endpoints may emerge during the course of the study and will be defined before second data base lock (following completion of the last visit (Day 360/ Month 12) by the last patient):

CCI





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IV. Study Design

A. Design Overview

This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess efficacy and safety of CDR132L in subjects with reduced LVEF ($\leq 45\%$) after MI. This study consists of a Screening Period (to occur at least 3 days after MI diagnosis), a 6-month Double-blind Period, and a 6-month Prolonged Follow-up Period with the End of Study (EOS) Visit at Day 360/Month 12. All subjects will be required to attend the study visits as described in the Schedule of Activities (SoA).

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Table 1 Schedule of Activities

Procedures	Screening Period (To occur at least 3 days after MI diagnosis)	Double-blind Period (Day 1 to Day 180/Month 6)							Prolonged Follow-up Period (6 months)
		Study Drug Treatment (Day 1, Day 29, and Day 57)				Follow-up			
Randomization (To occur no later than 14 days after MI diagnosis)		1	2	3	4	5	6	EOS/ET	
		Day 1 (pre-dose)	Days 2 to 5	Day 29	Day 57	Day 90	Day 180	Day 360	
				± 2	± 2	± 7	± 7	± 7	
				Month 1	Month 2	Month 3	Month 6	Month 12	
Visit									
Study Day									
Window (days)									
Month									
Informed consent	X								
Demographic data and medical history ^a	X ^a								
Inclusion/exclusion criteria	X								
Randomization		X							
Study drug administration ^b			X ^b		X	X			
Prior/concomitant medications	X		X	X	X	X	X	X	
EFFICACY									
Echocardiography ^c	X ^c					X	X	X	
KCCQ	X					X	X	X	
hs-cTn	X		X	X	X	X	X	X	
NT-proBNP	X ^d		X	X	X	X	X	X	
SAFETY									
Adverse event assessments	X		X	X	X	X	X	X	

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Procedures	Screening Period (To occur at least 3 days after MI diagnosis)	Double-blind Period (Day 1 to Day 180/Month 6)							Prolonged Follow-up Period (6 months)
		Study Drug Treatment (Day 1, Day 29, and Day 57)					Follow-up		
Randomization (To occur no later than 14 days after MI diagnosis)		1	2	3	4	5	6	EOS/ET	
		Day 1 (pre-dose)	Days 2 to 5	Day 29	Day 57	Day 90	Day 180	Day 360	
				± 2	± 2	± 7	± 7	± 7	
				Month 1	Month 2	Month 3	Month 6	Month 12	
Injection site reaction monitoring			X (post-dose)		X	X			
Physical examination	X		X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
12-lead electrocardiogram	X		X		X	X	X	X	X
Body weight	X			X	X	X	X	X	X
Hematology, biochemistry, coagulation ^c	X		X	X	X	X	X	X	
Urinalysis ^c	X		X		X		X	X	
EXPLORATORY EFFICACY									
CCI									

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Procedures	Screening Period (To occur at least 3 days after MI diagnosis)	Double-blind Period (Day 1 to Day 180/Month 6)							Prolonged Follow-up Period (6 months)
		Study Drug Treatment (Day 1, Day 29, and Day 57)				Follow-up			
Randomization (To occur no later than 14 days after MI diagnosis)		1	2	3	4	5	6	EOS/ET	
		Day 1 (pre-dose)	Days 2 to 5	Day 29	Day 57	Day 90	Day 180	Day 360	
				± 2	± 2	± 7	± 7	± 7	
				Month 1	Month 2	Month 3	Month 6	Month 12	
Visit									
Study Day									
Window (days)									
Month									
CCI									
Immunogenicity ^c			X		X	X		X	

Abbreviations: COVID-19 = coronavirus disease 2019; ECHO = echocardiography; ED = emergency department; EOS = end of study; ET = early termination; hs-cTn=high-sensitivity cardiac troponin; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro B-type natriuretic peptide; CCI

; MI = myocardial infarction; SoC = Standard of Care.

Note: All blood samples should be collected pre-dose at dosing days.

- Events and diseases will be recorded for up to 6 months prior to screening. COVID-19 infections and vaccinations will be recorded regardless of their time of occurrence.
- On Day 1 (preferably within one day after randomization but no later than 4 days after randomization) patients will receive CDR132L 5 mg/kg, CDR132L 10 mg/kg, or placebo IV. The second IV dose of the patient's assigned treatment will be administered on Day 29 ± 2 days, and the third IV dose on Day 57 ± 2 days. For doses administered in an outpatient setting, the patient should be observed for at least 30 minutes after dosing.
- The screening ECHO will be performed at least 3 days after MI diagnosis; all eligibility criteria must be confirmed no later than 14 days after MI diagnosis.
- At screening, sample is to be collected as early as possible preferably on the same day as the ECHO. NT-proBNP values required for eligibility confirmation may be collected at any time post MI either through medical history (e.g., site has collected it as SoC once the patient came to the hospital), through a local laboratory assessment, or by sending a sample to the central laboratory (if sites use the SoC sample or the local laboratory sample for eligibility confirmation, no additional sample for central laboratory assessment is needed).
- See [Appendix 3](#) in protocol for more information.

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Approximately 70 Investigators and study sites participated in this study. Approximately 280 subjects were enrolled/randomized into the study in a 1:1:1 ratio (approximately 90 subjects each, in 5 mg/kg, 10 mg/kg, and placebo groups). The study schema is presented in Figure 1.

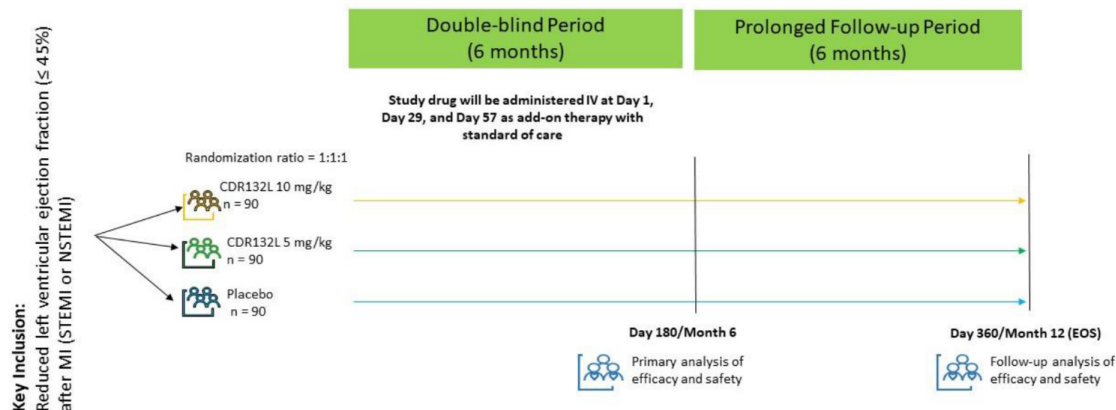


Figure 1 Study Schema

B. Sample Size Calculation

For the primary endpoint of percent (%) change from baseline LVESVI at month 6, a sample size calculation for the comparison of the two treatment arms (10 and 5 mg/kg CDR132L v.s. Placebo) is performed by using the two-sample t-test. The test level is set to 2.5% (one-sided). Assumptions are displayed in Table 2 below.

Test 1 (CDR132L 10 mg/kg v.s. Placebo)

$H_{01}: \mu_{T10} \leq \mu_P$ versus $H_{11}: \mu_{T10} > \mu_P$

Test 2 (CDR132L 5 mg/kg v.s. Placebo)

$H_{02}: \mu_{T5} \leq \mu_P$ versus $H_{12}: \mu_{T5} > \mu_P$

Left ventricular end-systolic index	Mean (change in %)	Standard deviation (%)	Power
Placebo response	1	9	
10 mg/kg	6	9	
5 mg/kg	5	9	
N = 90 per group	Step 1		96.0%
	Step 2		84.3%
	Overall		80.9%

Table 2 Sample Size Calculation Assumptions

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Step 1 (10 mg/kg versus placebo):

A sample size of 90 in each group will have 96.0% power to detect a difference in means of 5 (the difference between a Group 1 mean, μ_1 , of 6 and a Group 2 mean, μ_2 , of 1) assuming that the common standard deviation is 9 using a 2-group t-test with a 2.5% one-sided significance level.

Step 2 (5 mg/kg versus placebo):

A sample size of 90 in each group will have 84.33% power to detect a difference in means of 4 (the difference between a Group 1 mean, μ_1 , of 5 and a Group 2 mean, μ_2 , of 1) assuming that the common standard deviation is 9 using a 2-group t-test with a 2.5% one-sided significance level.

Including 90 subjects per group (270 total) will lead to a power of 96.0% for the first step (10 mg/kg vs placebo, difference in means of 5) and 84.3% for the second step (5 mg/kg vs placebo, difference in means of 4). In of the hierarchical test procedure, resulting in an overall power of at least 80 %. Ten additional subjects should be included to compensate for early dropouts.

C. Treatment Randomization

All subjects will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS/IXRS). Subjects will be randomly assigned in a 1:1:1 ratio to receive study treatment.

Randomization will be stratified by:

- Age groups (<60 years, ≥60 years)
- Location of infarction (anterior, non-anterior)

V. General Analytical Considerations

A. Data Sources

Data are recorded on electronic case report forms (eCRFs). Central laboratory data and ECHO data results will be provided via electronic data transfers (details in Protocol [Section 8.2.1](#)).

B. Definition of Baseline

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Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (first administration of study medication), including unscheduled assessments. In the case where the last non-missing measurement and the reference start date coincide, collection time, where available, will be compared with the first dose time to determine whether the measurement is pre-baseline or post-baseline. If time is not available, the measurement will be considered pre-baseline, but injection site reaction commencing on the reference start date will be considered post-baseline. If first dose date is not available, the randomization date for untreated subjects (or day 1 visit date for treated subjects) will be used as the proxy reference start date in defining baseline assessments.

Change from baseline is calculated as post-baseline values minus baseline values. Percentage (relative) change from baseline is calculated as ratio of change from baseline and baseline expressed as a percentage.

C. Analysis Visit Window

All efficacy and safety endpoints will be analyzed according to the nominal/assigned visits (as described in Protocol [Section 1.3](#)) except for assessments collected on early termination and unscheduled visits. Early termination (ET) and unscheduled visits will be re-numbered to analysis visits based on their windowed visits defined by actual study day in Table 3. If more than one visit or assessment (scheduled or unscheduled) occurs within a single visit window day and if one visit is scheduled and one is unscheduled, the assessment will take the scheduled one. If the two visits are equidistant from the target day and if both visits are scheduled or both are unscheduled, the visit with later date and time will be used.

Visit	Target Day	Analysis Window
Day 1	1	On or prior to Day 1
Days 2-5	3	Day 2 – Day 16
Day 29 / Month 1	29	Day 17 – Day 43
Day 57 / Month 2	57	Day 44 – Day 73
Day 90 / Month 3	90	Day 74 – Day 135
Day 180 / Month 6	180	Day 136 – Day 270
Day 360 / Month 12	360	Day 271 – Day 360

Table 3 Analysis Visit Window

Certain efficacy and safety endpoints are not scheduled to be assessed at each post-baseline. If the date of an ET or unscheduled visit does not fall into the analysis window of any scheduled visit, the assessment will be

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mapped to the scheduled post-baseline visit closest to the assessment date.

D. Missing Data

1. Partial and Missing Dates in AE and CM

Partial dates may be entered on the CRF for Adverse Events (AEs) and prior and concomitant medications (CMs). Dates from these forms will be reported in listings as collected without any imputation. However, reported partial information will be utilized in classification of TEAEs and prior and concomitant medications according to the rules described below.

- AEs that cannot be definitely determined as occurring prior to study drug administration will be counted as TEAEs unless either the partial start date/time or a partial or complete end date/time documents the AE as occurring prior to treatment.
- AE onset dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the month and year of first dosing of study drug, in which case the date will be assumed to be the date of first dosing of study drug and the AE will be considered as TEAE.
- AE onset dates with missing day and month will be assumed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the year of first dosing of the study drug, in which case the date will be assumed to be the date of the first dosing of study drug and the AE will be considered as TEAE.

Partial dates entered in the prior and CM form will be imputed for the purposes of determining whether the record is a concomitant or prior medication based on the following:

- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month
- Medications that are not ongoing and have a medication stop date with missing day and month will be assumed to occur on the last day of the non-missing year (i.e., December 31)

2. Missing Safety Data

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Sites will be instructed to especially pay attention to complete the safety section of the eCRF and if possible, collect to retrieve safety data among subjects who withdraw from the study early.

Missing safety data will not be replaced with imputed values, with the exception of missing severity or relationship to study medication for AE:

- Missing relationship to study medication will not be imputed and will be summarized as a separate “missing” category where applicable.
- Missing intensity will be summarized as a separate “missing” category.

3. Missing Efficacy Data

Sites will be instructed to minimize dropouts and if possible, collect to retrieve efficacy data among subjects who withdraw from the study early.

Missing efficacy data (including those due to early discontinuations) will be imputed by having the last non-missing visit value carried forward (LOCF) as detailed below.

For the primary efficacy endpoint and both LVEF (%) and NT-proBNP (pg/mL) secondary endpoints, multiple imputation (MI) based sensitivity analysis will be performed as detailed in [Section VII.B.3](#).

E. Multiple Study Centers

The centers will be considered as a covariance factor and added into the model for all analysis. The list of center groups for pooling the very small centers will be determined before unblinding.

F. Covariate Adjustment in Primary Analysis

Covariate adjustment will be addressed in relevant sections below, as appropriate.

G. Sample Size Reassessment

Not applicable.

H. Interim Analyses or Timing of Analyses

No interim analysis for efficacy is planned.

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Primary analysis will be done once the last subject has completed the 6-month time point (first database lock). Follow-up data after this time point will be analyzed separately once the last subject has completed last visit (Month 12; second database lock). A clinical study report will be written following the completion of the study (Day 360/Month 12).

A DSMB is implemented for this study and reviews unblinded safety data in format and frequency as described in a separate DSMB Charter.

I. Test Sizes

Any tested hypotheses will be tested against 1-sided alternatives, using procedures that provide an expected probability of Type I error (α) of 0.025 to show superiority.

J. Multiple Comparisons

For the primary efficacy endpoint, the comparison will be done for the 10 mg/kg dose group versus placebo, followed by 5 mg/kg versus placebo within a hierarchical two-step test procedure. The aim is to show superiority of the 10 mg/kg dose group (μ_{T10}) and the 5 mg/kg dose group (μ_{T5}) in comparison to placebo (μ_P) within a hierarchical test procedure with 2 steps:

Step 1

$H_{01}: \mu_{T10} \leq \mu_P$ versus $H_{11}: \mu_{T10} > \mu_P$,
where μ indicates the treatment effect in percent change from baseline. (i.e. $H_{01}: PCHG_{T10} \geq PCHG_P$ versus $H_{11}: PCHG_{T10} < PCHG_P$)

If Step 1 is successful, then proceed to Step 2. If Step 1 is not successful, then do not proceed to Step 2.

Step 2

$H_{02}: \mu_{T5} \leq \mu_P$ versus $H_{12}: \mu_{T5} > \mu_P$,
where μ indicates the treatment effect in percent change from baseline. (i.e. $H_{02}: PCHG_{T5} \geq PCHG_P$ versus $H_{12}: PCHG_{T5} < PCHG_P$)

To show superiority, the effect of CDR132L dose groups on the percent change in LVESVI must be larger (i.e., higher decrease in percent change from baseline) than the effect within the placebo group.

If both Step 1 and Step 2 are successful (i.e. statistically significant effects of both doses on the primary efficacy endpoint were established), then the following confirmatory secondary efficacy endpoints are tested on the

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pooled data of both doses (5 mg/kg and 10 mg/kg) against placebo to show the superiority:

- Change from baseline in LVEF (%) at Month 6
(H_{03a}: CHG_T ≤ CHG_P versus H_{13a}: CHG_T > CHG_P)
- Change from baseline in NT-proBNP (pg/mL) (on a logarithmic scale) at Month 6
(H_{03b}: CHG_T ≥ CHG_P versus H_{13b}: CHG_T < CHG_P)
- Change in ECHO:
 - strain analysis for global longitudinal strain (%) from baseline and at Month 6
(H_{03c}: CHG_T ≥ CHG_P versus H_{13c}: CHG_T < CHG_P)
- Well-being as evaluated by change from baseline at Month 6 in the following parameters:
 - Mean Kansas City Cardiomyopathy Questionnaire (KCCQ) score (i.e. Overall Summary score)
(H_{03d}: CHG_T ≤ CHG_P versus H_{13d}: CHG_T > CHG_P)

Control of the type I error rate across these secondary efficacy endpoints is achieved by application of the Hochberg procedure.

K. Analysis Populations

Three analysis populations will be used for various analyses. [Table 4](#) Analysis Sets illustrates the different populations and how these are defined.

Analysis Set	Description
Entered Analysis Set	All subjects who sign the informed consent form.
Intent-to-treat (ITT)	All subjects in the Entered Analysis Set who are randomized to study drug. Subjects will be analyzed according to their randomized study treatment.
Modified Intent-to-treat (mITT)	All randomized subjects who receive at least 1 dose of study drug (CDR132L or placebo). Subjects will be analyzed according to the treatment they were randomized to.



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Safety	All randomized subjects who receive at least 1 dose of study drug (CDR132L or placebo) and have at least 1 post-dose safety assessment. Subjects will be analyzed according to the treatment they actually received.
Per-protocol (PP)	<p>All subjects from ITT population that have completed treatment and 6-month visit without any major protocol deviations that could affect the validity of primary and secondary efficacy assessments. Subjects may be excluded from PP population due to any of the following criteria:</p> <ul style="list-style-type: none"> • Not compliant (in terms of study drug and study schedule) • Used prohibited therapies (as per protocol section 6.5.1) • Had other protocol violation that might affect the efficacy assessment <p>Per-protocol population will be determined by blinded review of data prior to unblinding. Subjects will be analyzed according to the treatment they actually received.</p>

Table 4 Analysis Sets

The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

Analysis Population	Type of Analysis				
	Subject Disposition	Baseline	Efficacy	Safety	Exposure/ Compliance
Entered Analysis Set	V				
ITT	V	V			
mITT	V	V	V		
Safety	V			V	V
Per Protocol	V	V	V		

Two observation periods are defined for each subject:

- In-trial: The in-trial period is defined as the time from the randomization to the date of last contact with the trial site.

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- On-treatment period: The on-treatment period is defined as the duration from the initial administration of the study treatment to the final administration. For the evaluation of adverse events (AEs), this period extends from the first administration of the study treatment to 30 days after the last administration.

L. Definition of Subgroups

A subgroup analysis for the primary endpoint of % change from baseline at Month 6 will be performed. The changes in LVESVI, LVEF (%), and NT-proBNP (pg/mL) from baseline (relative/absolute) at Month 6 and month 12 will be performed.

LVESVI, LVEF (%), and NT-proBNP (pg/mL) will be summarized descriptively by treatment group for the following prespecified subgroups. Further subgroups might be defined for additional exploratory analyses post hoc.

- Age group from CRF (less than 60 years, 60 years and older)
- Sex (Female, Male)
- MI type (STEMI, NSTEMI)
- Time of first treatment after MI event (d3-7 versus d7-14)
- Patients with and without treatment of SGLT2 inhibitors
- Disease severity acc. to
 - Killip class (Class I, Class II, Class III and Class IV)
 - NYHA class (Class I, Class II, Class III and Class IV)
 - LVEF (%) ($\leq$ median, $>$ median from mITT)
 - NT-proBNP (pg/mL) ($\leq$ median, $>$ median from mITT)
- Location of infarction (anterior, non-anterior)
- Diabetes Status (Diabetes/non-Diabetes)
- Troponin central baseline results ($\leq$ median, $>$ median from mITT)
- Chronic HF status (Patients with, Patients without)
 - Patients with chronic heart failure or reduced LVEF in medical history prior to MI index event.
- Renal function
 - eGFR (mL/min/1.72m²) Group 1 (" ≤ 45 ", " $>45, \leq 60$ ", " >60 ")
 - eGFR (mL/min/1.72m²) Group 2 (" ≤ 60 ", " >60 ")
- Atrial fibrillation status (Patients with, Patients without)
- Septum thickness ($\leq$ median, $>$ median from mITT)
 - The value will be obtained from an ECHO with the assessment 'Parasternal long axis view: Interventricular septum thickness.'

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M. Data Display Characteristics

Data displays produced for this study will include three types: summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. Data listings will not display subject initials.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

VI. Subject Accountability

A. Subject Characteristics

Demography and Baseline Characteristics. The data collected on the following characteristics will be summarized for ITT, mITT and PP populations by each treatment group:

- Age (years)
- Age group: <60, ≥60 years
- Sex at birth
- Race: White, Native Hawaiian or Other Pacific Islander, Black or African American, Asian, American Indian or Alaska Native, Not Reported
- Height (cm): Height measured at Screening visit will be reported.

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- Weight (kg): Weight measured at Screening visit will be reported.
- Body Mass Index (BMI): Calculated as body mass (kg) divided by the square of their height (m) with the unit of kg/m²
- Troponin I (ng/L) and Troponin T (ng/L) local results
- Time between MI diagnosis to Troponin local results (days)
- Killip class (Class I, Class II, Class III, Class IV)
- NYHA class (Class I, Class II, Class III and Class IV)
- LVEF (%) (<= median, > median)
- NT-proBNP (pg/mL) (<= median, > median)
- Stratification factors:
 - Age group at randomization: <60, ≥60 years
 - Location of infarction at randomization: anterior, non-anterior
- Diabetes Status (Diabetes/non-Diabetes)
- Troponin central baseline results (<= median, > median)
- Chronic HF status (Patients with, Patients without)
- Renal function
 - eGFR (mL/min/1.72m²) Group 1 ("<=45", ">45, <=60", ">60")
 - eGFR (mL/min/1.72m²) Group 2 ("<=60", ">60")
- Atrial fibrillation status (Patients with, Patients without)
- Septum size (hypertrophy) (<= median, > median)

A listing of the above characteristics will be presented for the ITT, mITT and PP population.

Myocardial Infarction history. The following MI related history will be summarized for the ITT population:

- Time between MI diagnosis to Randomization (days)
- Location of MI (anterior, posterior, lateral, other)
- Type (STEMI, NSTEMI)
- Number of previous infarctions (0, 1, 2, ≥3)

A listing of the above characteristics will be presented for the ITT population.

Medical History. Medical history (MH) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later. System Organ Class (SOC) and Preferred Term (PT) will be summarized by number and percentage of subjects having at least one occurrence of the event, for ITT population.

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COVID-19 Infection and Vaccination. The following information related to COVID-19 will be summarized for the ITT population:

- COVID-19 (Y, N) and if Yes:
 - Hospitalization due to COVID-19 (Y, N)
 - Long COVID-19 or post COVID-19 condition (Y, N)
- COVID-19 vaccination (Y, N)

B. Disposition

A summary of subjects will display the numbers (and percentages of the population) of subjects by treatment (as applicable) for the following:

- Subjects who provided informed consent (Entered Analysis Set)
- Subjects who fail screening, overall and by reason for screen failure
- Subjects randomized
- Subjects randomized who received at least one dose of study drug
- Subjects who complete treatment
- Subjects who discontinue treatment, overall and by reason for discontinuation
- Subjects who complete study
- Subjects who discontinue study, overall and by reason for discontinuation
- Subjects included in each analysis population (ITT, mITT, Safety, PP)
 - For PP population, the number of subjects who were excluded from PP (overall and by reason for exclusion) will also be summarized.

A listing by subject will display the details of screen failure reason of each screen failed subject. A listing of treatment and study completion information, including the reason for discontinuation, if applicable, will also be presented for all subjects in the ITT population.

C. Protocol Deviations

Major protocol deviations will be summarized for the ITT population with number (and percentage) of subjects in each protocol deviation category by treatment. In addition, a by-subject listing will be presented for details of all protocol deviations.

D. Visit Attendance

Subject visit attendance will be summarized at each visit, for the following:

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- Number and percentage of subjects who miss the visit
- Number and percentage of subjects who miss the visit due to non-compliance

VII. Efficacy Analyses

A. Efficacy Outcomes

Primary, secondary, and exploratory efficacy endpoints are described in [Section III](#). Additional definitions and derivations are as follows:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a patient reported 23-item questionnaire, which includes HF symptoms, impact on physical and social function, and how their HF impacts their quality of life within a 2-week recall period.

For the secondary efficacy outcome of change from baseline to Months 6 and 12 months in mean KCCQ score and mean scores of subdomains, the Overall Summary Score and subdomain scores (symptom burden, physical limitation, and quality of life) will be derived based on formula in [Appendix.A](#).

- Heart failure as assessed by time to first event of
 - Cardiovascular mortality
 - Hospitalization or emergency department visit(s) for HF conditions
- Cardiovascular and renal events as assessed by the time to the first event of the selected AE term (refer to [section VII.D](#) for details on the AE term).

The analysis of time to events is defined as time from first dose to the date of occurrence of the event of interest. Subjects who have discontinued without an event will be censored at the date of their last visit. Subjects that complete the study without an event will be censored at the end of the study (EOS/ET).

- NYHA class

The NYHA functional classification categorizes the extent of HF by placing subjects in one of 4 (I, II, III, IV) categories based on how

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much they are limited during physical activity and symptoms of shortness of breath and/or angina.

- ECG: QRS complex and ECG interpretation

B. Primary Efficacy Outcome Analysis

1. Primary Estimand

The primary estimand for establishing the efficacy of CDR132L consists of the mean difference in percent change from baseline in LVESVI at Month 6 among MI subjects randomized to either active treatment or placebo group calculated in the mITT analysis set, defined by the following attributes:

Attribute	Description
Treatments	CDR132L (5 mg/kg, 10 mg/kg) as an add-on to SoC vs placebo as an add-on to SoC
Population	Population of subjects with HF and reduced LVEF after MI, defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval
Variable	Percent change from baseline in LVESVI at Month 6
Population-level summary	Mean difference in percent change from baseline in LVESVI at Month 6
Intercurrent events	Treatment discontinuation, study discontinuation, death, (hospitalization for) CRT implants and heart transplantation; the treatment policy strategy will be used for the intercurrent events.

2. Primary Efficacy Analysis

The mITT Population will be the primary analysis population. The primary efficacy endpoint will also be analyzed using the PP population as supportive analysis.

The comparison of percent (%) change from baseline LVESVI at Month 6 will be done for the 10 mg/kg dose group versus placebo, followed by 5 mg/kg versus placebo within a hierarchical two-step test procedure. The aim is to show superiority of the 10 mg/kg dose group (μ_{T10}) and the 5 mg/kg dose group (μ_{T5}) in comparison to placebo (μ_P). The hierarchical testing procedure is described in [section V.J Multiple Comparisons](#).

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The percent change from baseline in LVESVI will be analyzed using an analysis of covariance (ANCOVA), with placebo acting as the reference. Individual ANCOVA models will be used for each test step, i.e. the 10 mg/kg and 5 mg/kg dose groups will be compared to placebo in separate models. The model will include treatment as a fixed effect and baseline LVESVI as a covariate. The analysis will also be adjusted for center group and the stratification factors of age group (<60 years, ≥60 years) and location of infarction (anterior, non-anterior). The least squares mean (LSM) estimates for each treatment arm will be displayed together with standard errors (SEs) and their corresponding 95% CIs. Treatment differences with 95% CIs will also be produced. The LSM line plot with ± one SE from the corresponding point estimate of the LS mean will be presented.

All observed data will be included in analysis regardless of intercurrent events. Missing post-baseline data through Month 6 will be imputed using the last observation (including baseline) carried forward (LOCF) approach. In addition, multiple imputations as described above will be used for sensitivity analyses.

Supportive analyses will be performed for PP population in a similar manner to the primary efficacy analysis.

For LVESVI, absolute change and % change from baseline will be summarized by treatment group and respective timepoint. A listing will present this information for each subject.

3. Sensitivity Analysis

Sensitivity Analysis 1: Analysis using Multiple imputation

Multiple imputation based sensitivity analysis will be performed. A reference (control) based imputation model will be applied based on the missing not at random (MNAR) assumption, according to the following steps:

- All the missing values will be multiply-imputed using the imputation model built from the placebo group, i.e., assuming the missing data in the treatment groups will have a profile that equals the profile of the placebo group for all timepoints. The missing data imputation will be implemented using PROC MI in SAS 9.4 with the MNAR statement. The variables to be used in the imputation model are treatment, center group, age (<60 years, ≥60 years), location of

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infarction (anterior, non-anterior), baseline LVESVI, and LVESVI values observed at post-baseline visits.

```
Proc mi data= indata seed=&seed nimpute=100 out= outdata;  
class trt01pn stratum1 stratum2 stratum3;  
var stratum1 stratum2 stratum3 base timepoint1 timepoint2;  
fcs reg(/details);  
mnar model(timepoint1 timepoint2/ modelobs=(trt01pn='0'));  
run;
```

Note: trt01pn='0' indicates placebo subjects.

- Once the competed datasets are formed, the same ANCOVA model as specified for the primary analysis will be applied to each completed set and inference drawn using PROC MIANALYZE.

A pre-specified seed number of 10272022 will be used in all imputation procedures as described above. Alternative model specifications may be used based on the actual data if there is an issue in model convergence.

Sensitivity Analysis 2: Analysis using Mixed model Repeated Measures (MMRM)

A MMRM model will be used to analyze the percent change from baseline using treatment group, analysis timepoint (Month 3 and Month 6), treatment group-by-month interaction, center group, age (<60 years, ≥60 years), location of infarction (anterior, non-anterior), baseline LVESVI as factors. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous first-order autoregressive covariance structure will be used as the first alternative, followed by the compound symmetry covariance structure and variance components covariance structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Any missing data are assumed to be missing at random.

The LSM for each treatment group with SE, LSM difference against placebo group with SE, 95% CI for the differences and the associated p-values will be presented at each analysis timepoint.

Sensitivity Analysis 3: Analysis using ANCOVA with pooled CDR132L group

Additionally, an ANCOVA analysis with the LOCF method will be performed for the pooled CDR132L group and the placebo group.

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C. Secondary Efficacy Analyses

For the following continuous change from baseline (absolute/relative) secondary endpoints:

- Change in LVEF (%) at Months 3, 6, and 12
- Change in NT-proBNP (pg/mL) (on a logarithmic scale) at Days 2 to 5, Months 1, 2, 3, 6, and 12
 - The Geometric Mean will be calculated by exponentiating the mean for each treatment, and the ratio will be also calculated by exponentiating the mean of the treatment difference.
- Change in LVESVI at Month 3, 6, and 12
- Change in Troponin T (ng/L) at Months 3, 6, and 12
- Change in KCCQ score (Overall Summary score) and subdomain scores (Physical Limitation, Symptom Burden, Quality of Life) at Months 6 and 12

A similar ANCOVA will be used, with placebo acting as the reference. The model will include treatment as a fixed effect and baseline value as a covariate. Also, the analysis will be adjusted for center group and the stratification factors of age group (<60 years, ≥60 years) and location of infarction (anterior, non-anterior).

Similar to the primary endpoint analysis, LOCF approach will be used for subjects that have missing data. No imputation will be performed for visits after Month 6. The PP population will also be used for LVEF (%) and NT-proBNP (pg/mL) secondary endpoints analysis.

Trellis plots and spider plots will be provided for NT-proBNP (pg/mL).

C.3. Testing strategy for the confirmatory secondary efficacy endpoints

Similar to the primary endpoint analysis, ANCOVA model with LOCF method will be used for absolute change from baseline in confirmatory secondary endpoints below at Month 6. The testing procedure is described in [section V.J. Multiple Comparisons](#).

- Absolute change from baseline in LVEF (%) at Month 6
- Absolute change from baseline in NT-proBNP (pg/mL) (on a logarithmic scale) at Month 6

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- Absolute change in ECHO:
 - strain analysis for global longitudinal strain (%) from baseline and at Month 6
- Well-being as evaluated by absolute change from baseline at Month 6 in the following parameters:
 - Mean Kansas City Cardiomyopathy Questionnaire (KCCQ) score (i.e. Overall Summary score)

C.4. Sensitivity Analysis

Sensitivity Analysis 1: Analysis using Multiple Imputation

Similar to the primary endpoint analysis, MI method will be used for change from baseline at Month 6 with the endpoints below.

For the LVEF (%) endpoint, the variables to be used in the imputation model are treatment, center group, age (<60 years, ≥60 years), location of infarction (anterior, non-anterior), baseline LVEF (%), and LVEF (%) values observed at post-baseline visits.

For the NT-proBNP (pg/mL) endpoint, the variables to be used in the imputation model are treatment, center group, age (<60 years, ≥60 years), location of infarction (anterior, non-anterior), baseline NT-proBNP (pg/mL), and NT-proBNP (pg/mL) values observed at post-baseline visits.

Sensitivity Analysis 2: Analysis using Mixed model Repeated Measures (MMRM)

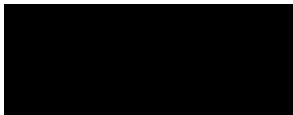
Similar to the primary endpoint analysis, MMRM model will be used for change from baseline with the endpoints below.

The treatment group, analysis timepoint (Month 3 and Month 6), treatment group-by-month interaction, center group, age (<60 years, ≥60 years), location of infarction (anterior, non-anterior), baseline LVEF (%) will be included in the MMRM model for LVEF (%) analysis.

The treatment group, analysis timepoint (Month 1, Month 2, Month 3 and Month 6), treatment group-by-month interaction, center group, age (<60 years, ≥60 years), location of infarction (anterior, non-anterior), baseline NT-proBNP (pg/mL) will be included in the MMRM model for NT-proBNP (pg/mL) analysis.

D. Exploratory Efficacy Analysis

CCI

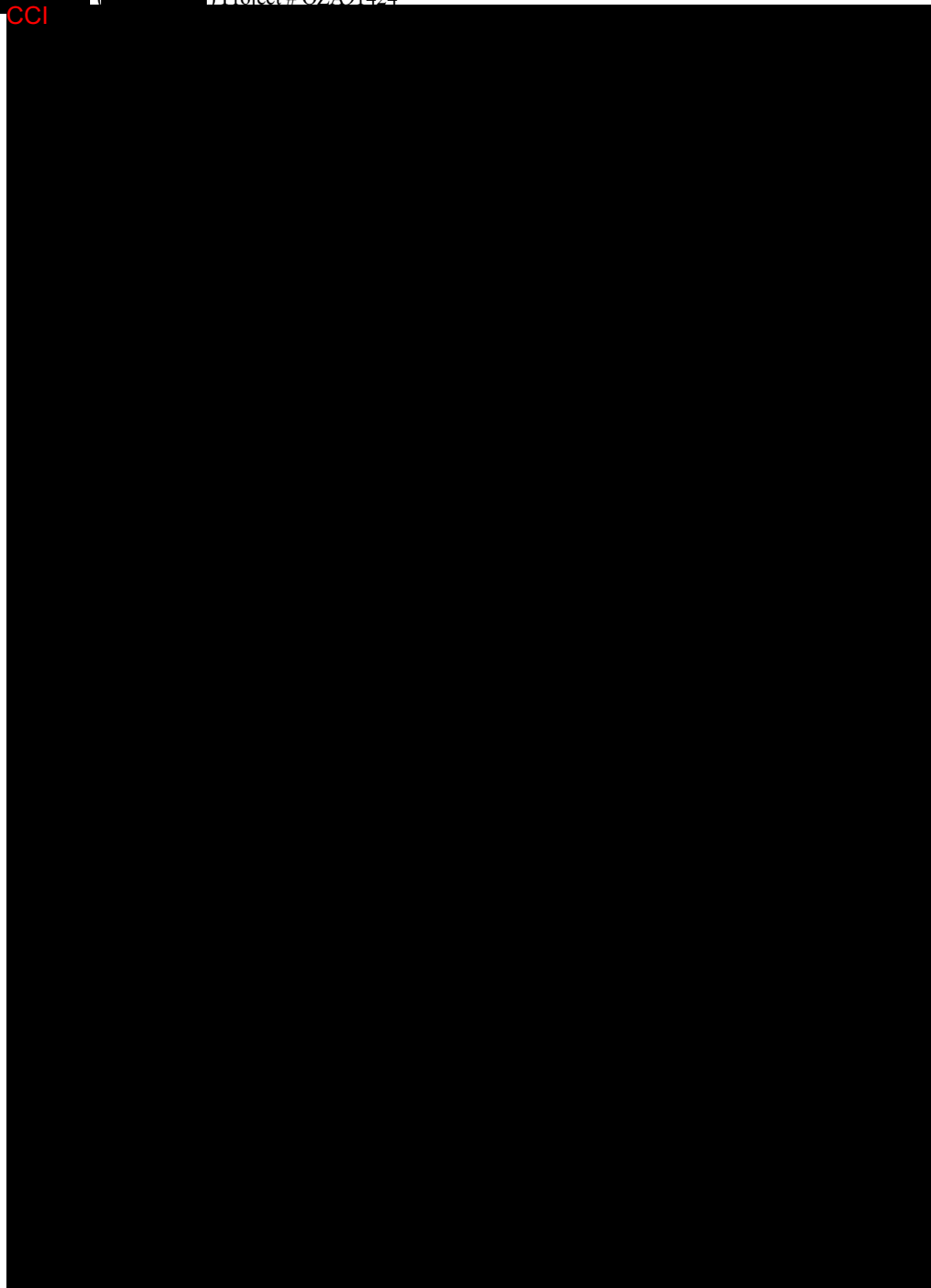


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CCI



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CCI

E. Subgroup analyses

Subgroup analyses based on age group, sex, MI type, time of first treatment after MI event, patients with and without treatment of SGLT2 inhibitors and disease severity as defined in [section V.L](#) may also be performed in an exploratory manner for secondary [LVESVI, LVEF (%) and NT-proBNP (pg/mL)] endpoints.

VIII. Safety Analyses

All safety analyses will be based on the Safety Population. No formal statistical analysis of the safety data will be performed.

A. Exposure

Exposure to the treatment will be summarized by group, for each dosing visit and overall, in terms of the following:

- number of doses administered
- administered dose (mL)
- % planned dose administered
 - $(\text{administered dose} / \text{planned dose (24 mL)}) * 100$

Cases where reduced dose has been infused, as well as cases of infusion interruption, will be summarized along with the reason that has been reported (AE, other). This information will also be presented as a by-subject listing.

B. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher.

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Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first administration of study treatment and prior to 30 days after the last administration of study treatment.

AE is considered treatment-related if the relationship to the study drug is "related"; if relationship to study treatment is missing, the event will be summarized as a separate "missing" category. Missing severity will be summarized as a separate "missing" category.

The following AE information will be summarized by treatment group:

- All TEAEs
- Treatment related TEAEs
- SAEs
- Serious TEAEs
- Serious Treatment-related TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to death
- Adverse events of special interest (AESIs)
- Injection site reactions

The following AE summaries will be produced by SOC (alphabetical order) and PT (descending order of the overall frequency):

- TEAEs
- TEAEs by maximum severity (mild, moderate, severe). TEAEs missing a severity grade will be reported in a separate "missing" category.
- Treatment Related TEAEs
- SAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to deaths

AEs will be summarized with the number of patients, percentage of patients, number of events, and the rate of events.

The rate of events is calculated as (number of events / patient years of exposure), where patient years of exposure = (last dose date – first dose date + 31) / 365.25.

At each level of summarization, a patient will be counted once if he/she reported one or more events. The severity grade and relationship to study drug will be summarized in a similar manner.

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All AEs will be presented in a by-subject listing, detailing in the verbatim term given by the investigator, PT, SOC, start date/time, end date/time or ongoing, seriousness, intensity grade, outcome, relationship to study drug, action taken with study drug, and other action taken.

C. Clinical Laboratory Results

Quantitative laboratory test variables (including hematology, coagulation, serum chemistry, and urinalysis) will be summarized by treatment group and visit (as per SOA in Protocol [Section 1.3](#)) using descriptive statistics; number and percentage of subjects with normality status (low, normal and high) will also be summarized. Laboratory tests with categorical results (e.g., urinalysis) will be summarized by treatment group and visit by the number of subjects in each category.

Shift tables (low, normal, high according to the normal range criteria) between baseline and post-baseline time points will be presented by laboratory test and treatment group.

Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized but will be listed.

Trellis plots (line plots over time) and scatter plots (Baseline v.s Max post-baseline) will be provided for chemistry, hematology, and coagulation. Additionally, spider plots will be provided for kidney tests, liver tests, and thrombocytes.

D. Vital Signs

Descriptive statistics of vital signs will be summarized for each treatment group using descriptive statistics at each visit for absolute values and change from baseline values (as per SOA in Protocol [Section 1.3](#)). Additionally, spider plots will be provided.

The following variables will be included:

- Body temperature (°C)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiratory rate (beats/min)
- Pulse rate (beats/min)

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- Normality status (normal, abnormal with clinical significance, or abnormal without clinical significance)

All vital sign variables will be presented in a by-subject listing for all recorder visits.

E. 12-Lead Electrocardiogram (ECG)

Descriptive statistics of ECG will be summarized for each treatment group using descriptive statistics at each visit for absolute values and change from baseline values (as per SOA in Protocol [Section 1.3](#)). Additionally, spider plots will be provided.

The following variables will be included:

- Heart rate (beats/min)
- PR (msec)
- QRS (msec)
- QT uncorrected (msec)
- QTcF interval (msec)

F. Physical Examination

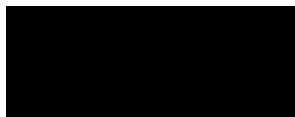
Clinically important abnormal physical examination results will be recorded as MH or AEs and analyzed accordingly. Subjects with abnormal physical examination will be presented in a by-subject listing.

G. Concomitant Medications

For analysis purposes, the start and stop dates of the medications will be used to determine the prior and concomitant medications based on the definition below. Prior medications are defined as medications with start and stop times prior to the time of study drug administration. Concomitant medications are defined as medications with a start time at or after the time of study drug administration or medications with a start time prior to study drug administration but continuing after treatment.

Prior and Concomitant Medications will be coded using the WHO Drug version B3 Global March 2022 or later. The number and percentage of subjects with prior or concomitant medications will be summarized by WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification level 4 or highest level available, and preferred term (PT) for each treatment.

Concomitant Medication(s) information will be presented in a by-subject listing for all recorder visits.

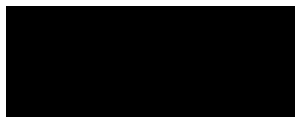


Statistical Analysis Plan

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H. Immunogenicity Analysis

Immunogenicity evaluation will be performed by a specialty laboratory after completion of the study. This analysis and results will be covered in a separate report.



Statistical Analysis Plan

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IX. References

Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons; 9 June 2004.

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands And Sensitivity Analysis in Clinical Trials Guidance for Industry

Multiple Endpoints in Clinical Trials Guidance for Industry. October 2022.

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X. Appendix

A. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The 23-item KCCQ questionnaire contains 7 domains which include the following:

- Physical Limitation (6 items)
- Symptom Stability (1 item)
- Symptom Frequency (4 items)
- Symptom Burden (3 items)
- Self-Efficacy (2 items)
- Quality of Life (3 items)
- Social Limitations (4 items)

All items are measured on a Likert scale with 5–7 response options. In addition, three summary scores are calculated:

- Total Symptom score (average of Symptom Frequency and Symptom Burden)
- Clinical Summary score (average of Physical Limitation and Total Symptoms)
- Overall Summary score (average of Physical Limitation, Total Symptoms, Quality of Life, and Social Limitation)

The individual item responses and domains scores will be calculated per the table below:

Scale	Item Number	Original response
Physical Limitation	1a to 1f	Extremely limited = 1 Quite a bit limited = 2 Moderately limited = 3 Slightly limited = 4 Not at all limited = 5 Limited for other reasons or did not do = missing
	Step 1: The original response needs to be transferred to the score value using the formula below: $S = [(Questions) - 1]/4$	
	Step 2: If at least three of scores are not missing: Physical Limitation Score = $100 * (\text{mean of available S results})$	
Symptom Stability	2	Much worse = 1 Slightly worse = 2 Not changed = 3 Slightly better = 4 Much better = 5 I've had no symptoms over the last 2 weeks = 3
	Step 1:	



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Symptom Frequency	The original response needs to be transferred to the score value using the formula below: $S = [(Questions) - 1]/4$	
	Step 2: If the score is not missing: Symptom Stability Score = $100 * (\text{mean of available S result})$	
	3,5,7,9	<u>Question 3</u> Every morning = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past 2 weeks = 5 <u>Questions 5 and 7</u> All of the time = 1 Several times a day = 2 At least once a day = 3 3 or more times a week but not every day = 4 1-2 times a week = 5 Less than once a week = 6 Never over the past 2 weeks = 7 <u>Question 9</u> Every night = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past 2 weeks = 5
	Step 1: $S3 = [(Question\ 3) - 1]/4$ $S5 = [(Question\ 5) - 1]/6$ $S7 = [(Question\ 7) - 1]/6$ $S9 = [(Question\ 9) - 1]/4$	
Symptom Burden	Step 2: If at least two of scores are not missing: Symptom Frequency Score = $100 * (\text{mean of S3, S5, S7 and S9})$	
	4,6,8	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3 Slightly bothersome = 4 Not at all bothersome = 5 I've had no swelling/fatigue/shortness of breath = 5
	Step 1: The original response needs to be transferred to the score value using the formula below: $S = [(Questions) - 1]/4$	
Self-Efficacy	Step 2: If at least one of scores is not missing: Symptom Burden Score = $100 * (\text{mean of S4, S6 and S8})$	
	10, 11	<u>Question 10</u>

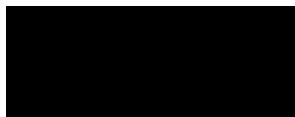


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		<p>Not at all sure = 1 Not very sure = 2 Somewhat sure = 3 Mostly sure = 4 Completely sure = 5</p> <p><u>Question 11</u> Do not understand at all = 1 Do not understand very well = 2 Somewhat understand = 3 Mostly understand = 4 Completely understand = 5</p>
		<p>Step 1: The original response needs to be transferred to the score value using the formula below: $S = [(Questions) - 1]/4$</p>
		<p>Step 2: If at least one of score is not missing: Self-Efficacy Score = $100 * (\text{mean of S10 and S11})$</p>
Quality of Life	12, 13, 14	<p><u>Question 12</u> It has extremely limited my enjoyment of life = 1 It has limited my enjoyment of life quite a bit = 2 It has moderately limited my enjoyment of life = 3 It has slightly limited my enjoyment of life = 4 It has not limited my enjoyment of life at all = 5</p> <p><u>Question 13</u> Not at all satisfied = 1 Mostly dissatisfied = 2 Somewhat satisfied = 3 Mostly satisfied = 4 Completely satisfied = 5</p> <p><u>Question 14</u> I felt that way all of the time = 1 I felt that way most of the time = 2 I occasionally felt that way = 3 I rarely felt that way = 4 I never felt that way = 5</p>
		<p>Step 1: The original response needs to be transferred to the score value using the formula below: $S = [(Questions) - 1]/4$</p>
		<p>Step 2: If at least one of scores is not missing: Quality of Life Score = $100 * (\text{mean of S12, S13 and S14})$</p>
Social Limitations	15a to 15d	<p>Severely limited = 1 Limited quite a bit = 2 Moderately limited = 3 Slightly limited = 4 Did not limit at all = 5</p>



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	Does not apply or did not do for other reasons = Missing
	Step 1: The original response needs to be transferred to the score value using the formula below: $S = [(Questions) - 1]/4$
	Step 2: If at least two of scores are not missing: Social Limitations Score = $100 * (\text{mean of S15a to 15d})$



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Browsers:	<ul style="list-style-type: none">• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above.• Windows Edge Current Version• Mozilla Firefox Current Version• Safari (Mac OS only) 6.2 or above• Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	<ul style="list-style-type: none">• Apple iOS 7.0 or above• Android 4.0 or above

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