ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3139

STUDY DESIGN

Efficacy and safety of CDR132L in patients with reduced left ventricular ejection fraction after myocardial infarction: Rationale and design of the HF-REVERT trial

Johann Bauersachs[1]*, Scott D. Solomon[2], Stefan D. Anker[3], Isabel Antorrena-Miranda[4], Sandor Batkai[5], Janika Viereck[5], Steffen Rump[5], Gerasimos Filippatos[6], Ulrich Granzer[7], Piotr Ponikowski[8], Rudolf A. de Boer[9], Orly Vardeny[10], Wilfried Hauke[5], and Thomas Thum[5,11]*

[1]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; [2]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Department of Cardiology (CVK) of German Heart Center Charité, BIH Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany; [4]Cardiology Department, Hospital Universitario la Paz-Idipaz, Madrid, Spain; [5]Cardior Pharmaceuticals GmbH, Hannover, Germany; [6]Department of Cardiology, School of Medicine, Athens University Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece; [7]Granzer Regulatory Consulting & Services GmbH, Munich, Germany; [8]Institute of Heart Diseases, University Hospital, Medical University Wroclaw, Wroclaw, Poland; [9]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; [10]University of Minnesota Medical School, Minneapolis, MN, USA; and [11]Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany

Received 2 September 2023; revised 25 November 2023; accepted 30 December 2023

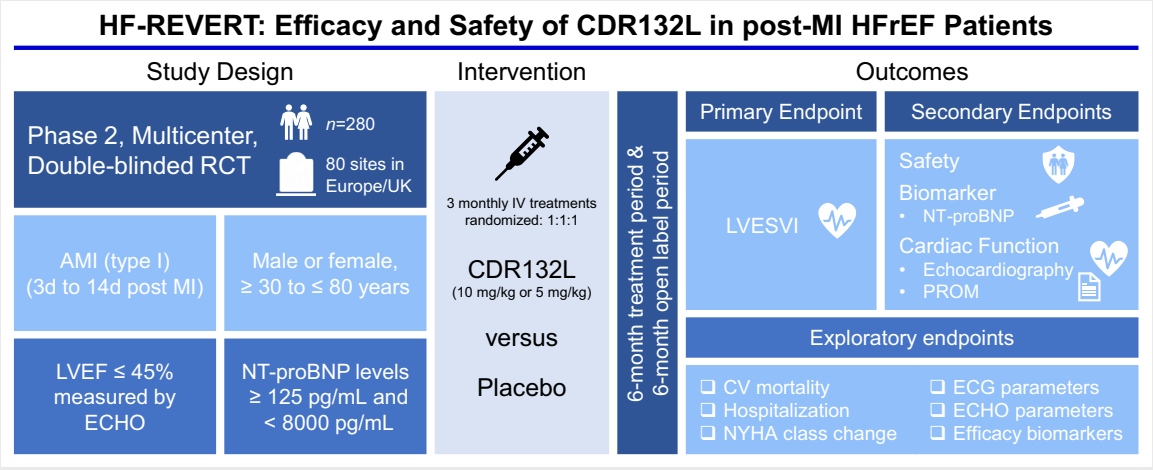
Aim Inhibition of microRNA (miR)-132 effectively prevents and reverses adverse cardiac remodelling, making it an attractive heart failure (HF) target. CDR132L, a synthetic antisense oligonucleotide selectively blocking pathologically elevated miR-132, demonstrated beneficial effects on left ventricular (LV) structure and function in relevant preclinical models, and was safe and well tolerated in a Phase 1b study in stable chronic HF patients. Patients with acute myocardial infarction (MI) and subsequent LV dysfunction and remodelling have limited therapeutic options, and may profit from early CDR132L treatment.

Methods The HF-REVERT (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 after Myocardial Infarction) evaluates the efficacy and safety of CDR132L in HF patients post-acute MI ($n = 280$), comparing the effect of 5 and 10 mg/kg CDR132L, administered as three single intravenous doses 28 days apart, in addition to standard of care. Key inclusion criteria are the diagnosis of acute MI, the development of systolic dysfunction (LV ejection fraction ≤45%) and elevated N-terminal pro-B-type natriuretic peptide. The study consists of a 6-month double-blinded treatment period with the primary endpoint LV end-systolic volume index and relevant secondary endpoints, followed by a 6-month open-label observation period.

Conclusion The HF-REVERT trial may underpin the concept of miR-132 inhibition to prevent or reverse cardiac remodelling in post-MI HF. The results will inform the design of subsequent outcome trials to test CDR132L in HF.

*Corresponding author. Johann Bauersachs, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany. Tel: +49 511 5323841, Fax: +49 511 5325412, Email: bauersachs.johann@mh-hannover.de
Thomas Thum, Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany. Tel: +49 511 5325272, Fax: +49 511 5325274, Email: thum.thomas@mh-hannover.de

Graphical Abstract



Study design and intended outcomes of the HF-REVERT study with CDR132L, a synthetic antisense oligonucleotide inhibitor selectively targeting microRNA-132, in patients with reduced left ventricular ejection fraction (LVEF) after myocardial infarction (MI). AMI, acute myocardial infarction; CV, cardiovascular; ECG, electrocardiogram; ECHO, echocardiography; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVESVI, left ventricular end-systolic volume index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PROM, patient-reported outcome measure; RCT, randomized clinical trial.

Keywords Phase 2 trial design • CDR132L • Post-myocardial infarction heart failure • Contractile function • Cardiac remodelling • microRNAs

Introduction

Despite proven efficacy of pharmacotherapies, heart failure (HF) is still a growing pandemic with an estimated prevalence of 64.34 million cases, contributing to 9.91 million years lost to disability.[1] Patients with acute myocardial infarction (MI) are at high risk for both developing early and progressive HF or cardiac death, particularly if the acute MI is complicated by left ventricular (LV) systolic dysfunction.[2–4] HF complicating MI is common and is a powerful predictor of death.[5,6] The incidence of early HF among patients hospitalized for MI varies between 14% and 36%.[4,7] In a recent retrospective analysis (RECORD-MI) of patients with acute MI, 31.3% of patients with no prior history of HF developed new-onset HF during the hospitalization (1578 out of 5047), and the 1-year mortality rate for those were 11%, while only 5% for those who did not develop HF.[8]

The characteristic common pathological feature of HF after MI is adverse structural LV remodelling,[9] in response to mechanical stress and neurohormonal activation that was initially considered irreversible. Cardiac reverse remodelling, a process by which the failing myocardium normalizes chamber geometry and function with correction of molecular and transcriptional abnormalities, may be achieved secondarily to some degree by guideline-directed medical therapy (GDMT).[10] However, we still lack therapies with proven long-term efficacy in patients with HF following acute MI that primarily directly affect cardiac tissue and thereby reversing adverse remodelling.

In the PARADISE-MI trial,[11] the angiotensin receptor–neprilysin inhibitor sacubitril/valsartan missed its primary endpoint to reduce the risk of cardiovascular death and HF hospitalizations after an acute MI. Similarly, the brain aminopeptidase A inhibitor firibastat in post-MI HF patients failed to show efficacy in a recent Phase 2 trial.[12] In another small Phase 2 trial, the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin given in addition to GDMT post-MI resulted in a significant N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction over placebo.[13] Currently, two large ongoing trials, DAPA-MI[14] and EMPACT-MI,[15] have been testing whether dapagliflozin and empagliflozin, respectively, can lower the risk for HF hospitalization and death in patients with cardiac dysfunction after MI. The DAPA-MI trial, a large international registry-based, randomized, double-blind trial, enrolling 4017 patients without prior diabetes or chronic HF, presenting with acute MI and impaired LV systolic function, found no impact on the composite of cardiovascular death and/or hospitalization for HF in patients with acute MI, after approximately 1 year of treatment with dapagliflozin compared to placebo. However, there were significant benefits with regard to improvement in cardiometabolic outcomes (which were mainly driven by weight loss).[16]

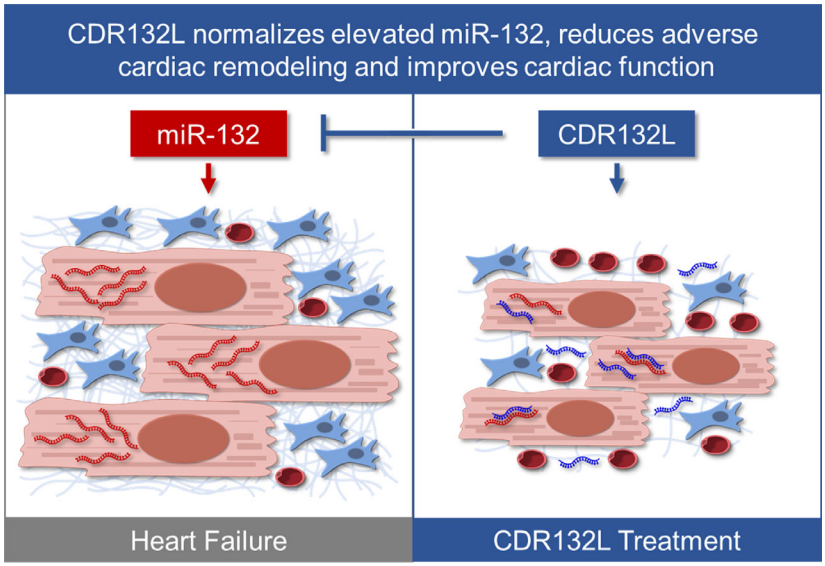


Figure 1 CDR132L's mode of action. In response to pathophysiological stress such as myocardial infarction or excessive mechanical load, expression of miR-132 is increased imbalancing cellular signalling and provoking detrimental morphological changes that impair cardiac function. Treatment with the antisense oligonucleotide inhibitor CDR132L has the potential to halt and reverse adverse remodelling by blocking and inactivating excessive miR-132 that reduces pathological hypertrophic cardiomyocyte growth, cardiac fibrosis, capillary rarefaction, and finally improves systolic and diastolic function of the heart.

Overexpression of microRNA-132-3p (miR-132) in cardiac cells is causally related to cardiac remodelling and HF progression. miR-132 is a central switch in cardiac cells affecting the expression of its molecular targets, such as by inhibition of transcription factors (e.g. the regulator of anti-hypertrophic FoxO3) and of calcium handling genes (e.g. calcium transporter and ATPase SERCA2A), along with the activation of the calcineurin/NFAT signalling pathway, all of which are crucially involved in maladaptive cardiac remodelling, transformation, and pathological cardiac growth (hypertrophy), contributing to adverse cardiac remodelling and HF.[17–20] Thus, blocking pathologically elevated miR-132 expression is suited to reverse ischaemic and non-ischaemic adverse cardiac remodelling and to restore normal cellular functions, contributing to improved cardiac performance in HF patients (*Figure 1*).

RNA therapeutics have become an attractive pharmacological approach modulating novel targets, including non-coding RNAs such as microRNA. Several antisense oligonucleotide (ASO) based microRNA inhibitors successfully reached early clinical development underscoring the robustness of this rechnology.[21] CDR132L is a synthetic ASO selectively blocking miR-132.[18] Inhibition of miR-132 effectively prevents and reverses HF in large animal models, and translational *in vitro* and *in vivo* studies have demonstrated meaningful efficacy of CDR132L in HF.[17–20] Several completed pre-clinical large animal studies assessing pharmacodynamics revealed that CDR132L treatment significantly improves both systolic and diastolic cardiac function and reverses adverse cardiac remodelling in both ischaemic (post-MI HF) and non-ischaemic models of HF.[17–20] CDR132L was well tolerated throughout pre-clinical models. Non-clinical pharmacokinetic (PK), safety pharmacology and toxicology studies of CDR132L have demonstrated that monthly dosages up to 10 mg/kg provides sufficient tissue exposure and the safety profile is adequate to progress with clinical development. A recent first-in-human study in 28 patients with stable HF (New York Heart Association [NYHA] class I to III) of ischaemic origin reported CDR132L to be safe and well tolerated.[22] The study determined the effects of four dose levels: 0.32, 1, 3, and 10 mg/kg of CDR132L administered intravenously (IV) on days 1 and 28 as an add-on to standard of care (SoC). Importantly, in that study first hints of efficacy could be demonstrated such as reductions in NT-proBNP plasma levels in the higher dose groups. Some pharmacodynamic (PD) evaluation revealed first trends of efficacy in HF relevant parameters (e.g. LVEF, HF-related biomarkers) supporting further clinical assessment of CDR132L in various HF conditions.

The potential mechanistic effects of miR-132 inhibition by CDR132L may be particularly beneficial in acute MI patients with myocardial dysfunction, potentially reversing adverse remodelling (*Figure 1*), based on the convincing non-clinical efficacy data in acute and chronic post-MI large animal HF models.[17,18] MI patients presenting early systolic dysfunction have been relatively understudied and therapeutic options are limited. The HF-REVERT (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 After Myocardial Infarction) is a proof-of-concept study and will evaluate the efficacy of CDR132L in improving cardiac function and safety in patients with reduced LVEF (≤45%) for 12 months post-MI. Herein, we describe the design of the HF-REVERT trial.

Trial design and methods

HF-REVERT is an international, multicentre, Phase 2, randomized, double-blind, placebo-controlled trial. This Phase 2 study aims to assess the efficacy and safety of CDR132L at 5 mg/kg and 10 mg/kg, given as three single IV doses administered 28 days apart as an add-on to SoC therapy, in a larger cohort of patients ($n = 280$) with HF and an LVEF ≤45% after MI with a follow-up of 12 months. The trial has been registered on ClinicalTrials.gov: NCT05350969,[23] and independent ethics committees approved the clinical protocol at each participating centre. The trial is conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provide written informed consent before study entry. The study design and key outcomes are summarized in the *Graphical Abstract* and *Table 1*.

Patients

The eligibility criteria for HF-REVERT are summarized in *Table 2*. Briefly, key inclusion criteria are spontaneous acute MI (diagnosis within 14 days before randomization) and the development of systolic dysfunction (LVEF ≤45%) after ST-elevation MI (STEMI) diagnosis, or patients with non-STEMI (NSTEMI) with evidence of significant myocardial necrosis (elevated troponin T or I). Elevated NT-proBNP level is an additional eligibility requirement (NT-proBNP ≥125 pg/ml and <8000 pg/ml). Patients, both, male and female of non-child bearing potential, required to be aged ≥30 to ≤80 years.

Key exclusion criteria are patients with HF of non-ischaemic origin, e.g. myocarditis, alcoholic cardiomyopathy, patients with history of decompensated HF, NYHA class IV, severe valvular heart disease or a history of LVEF <30% within 6 months prior to the index event or any clinically significant abnormalities in the electrocardiogram (ECG). Also, patients with systolic hypo- or hypertension, patients with an estimated glomerular filtration rate <30 ml/min/1.73 m^2 or on dialysis, patients with impaired liver function or hepatic insufficiency, or patients with medical history of bleeding disorders or thrombocytopenia.

It is planned that patients will be recruited from approximately 80 sites in seven European countries and in the UK. The first patient was enrolled on 11 July 2022.

Study design

This study consists of a 6-month double-blind treatment period followed by a 6-month open-label period. Suitable patients will be screened to determine eligibility at least 3–14 days after MI diagnosis.

Table 1 HF-REVERT trial summary

Trial design	This is a Phase 2, multicentre, randomized, parallel, three-arm, placebo-controlled study in patients with reduced LVEF (≤45%) post-MI treated testing two doses of CDR132L against placebo in addition to standard of care: • CDR132L 10 mg/kg body weight IV in single dose on day 1, day 29 and day 57 • CDR132L 5 mg/kg body weight IV in single dose on day 1, day 29 and day 57 • Placebo IV in single dose on day 1, day 29 and day 57 Enrols 280 randomized patients at up to 80 sites in Europe and UK This study comprises a screening period (to occur at least 3 days after MI diagnosis), a 6-month double-blind period, and a 6-month extension period with the EOS visit at day 360/month 12
Objective	To test the safety and efficacy of CDR132L, a synthetic ASO and selective inhibitor of miR-132, in post-MI HFrEF patients
Hypothesis	Repeated CDR132L treatment of post-MI HFrEF patients will be safe and effective
Primary endpoint	Efficacy: • LVESVI measured by echocardiography, change between baseline and month 6
Secondary endpoints	Safety: • Clinical laboratory assessment, vital signs, physical examination, and ECGs Efficacy: • NT-proBNP • Echocardiographic parameters • Patient-reported outcomes (KCCQ) Changes between baseline and month 6
Exploratory endpoints	• Cardiovascular mortality • Hospitalization • Change in NYHA class • ECG parameters • Echocardiography parameters • Pharmacodynamic and target engagement biomarkers

ASO, antisense oligonucleotide; ECG, electrocardiogram; EOS, end of study; HFrEF, heart failure with reduced ejection fraction; HF-REVERT, Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction after Myocardial Infarction; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Table 2 Inclusion and exclusion criteria of the HF-REVERT study

Inclusion criteria	• Male or female patients between ≥30 to ≤80 years at the date of signing informed consent
	• Spontaneous acute MI (AMI type I, STEMI, or NSTEMI) based on the universal MI definition with randomization to occur no later than 14 days after index event diagnosis
	• LVEF ≤45% as measured by echocardiography after MI diagnosis
	• Body weight of ≤120 kg
	• NT-proBNP level ≥125 pg/ml and <8000 pg/ml at screening
Exclusion criteria	• Women of childbearing potential
	• HF patient of non-ischaemic origin; e.g. myocarditis, alcoholic cardiomyopathy
	• History of decompensated HF or a history of LVEF <30% within 6 months prior to the screening period
	• NYHA class IV at screening or randomization
	• Planned cardiac intervention (angiogram without angioplasty is acceptable) or any other planned surgery after the screening period
	• Severe valvular heart disease
	• Systolic BP <90 mmHg or >180 mmHg, diastolic BP <50 mmHg or >110 mmHg, and/or heart rate <50 or >100 bpm at screening or randomization
	• Estimated glomerular filtration rate <30 ml/min/1.73 m^2 or on dialysis
	• Hepatic insufficiency classified as Child–Pugh B or C
	• Known active human immunodeficiency virus, hepatitis B, or hepatitis C infection at screening
	• Impaired hepatic function defined by a total bilirubin level of ≥2 x the ULN and ALT levels ≥3 x ULN
	• Medical history of disease(s) affecting the blood–brain barrier, e.g. stroke within 6 months or multiple sclerosis
	• Medical history of bleeding disorders or has thrombocytopenia (platelets <100 000/µl)
	• Poorly controlled diabetes as determined by the investigator
	• Patient is currently on treatment for epilepsy
	• Current or relevant history of physical or psychiatric illness that is/are not stable or may require a change in treatment, use of prohibited therapies during the study, or cause the patient to be unlikely to fully comply with the requirements of the study or complete the study, or any condition that presents undue risk from the study drug or study procedures
	• History or presence of any of the following cardiac conditions: known structural cardiac abnormalities beyond HF, family history of long QT syndrome, cardiac syncope, or recurrent, idiopathic syncope
	• Any clinically significant abnormalities, at the discretion of the investigator, in rhythm, conduction, or morphology of resting ECG that pose an additional safety risk to patients
	• Active SARS-CoV-2 infection confirmed as per the local testing guidelines at screening
	• Patient has other significant disease or disorder which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence the result of the study or the patient's ability to participate in the study
	• Patients received an investigational product or treated with an investigational device within 90 days prior to first study drug administration
	• Patient has known or suspected intolerance or hypersensitivity to the study drug, any closely related compound, or any of the stated ingredients
	• Patient is not to be enrolled into the study if they received any prohibited therapy within 3 months of screening (including anticancer therapy [chemo-, immune-, radio-, targeted, or gene therapy] and any other investigational agents)
	• Patient is involved in the planning and/or conduct of the study (applies to sponsor staff, staff at the study site, and third-party vendors)

AMI, acute myocardial infarction; ALT, alanine aminotransferase; BP, blood pressure; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STEMI, ST-elevation myocardial infarction; ULN, upper limit of normal.

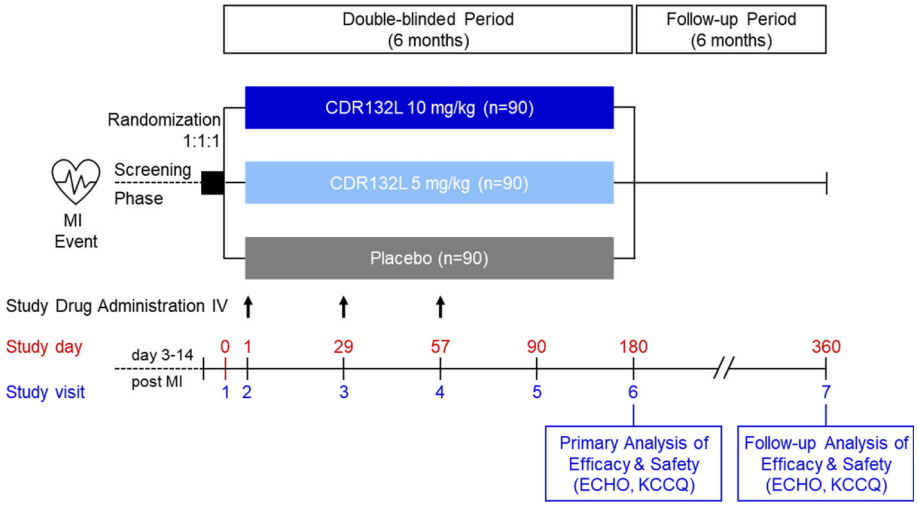


Figure 2 Design of the HF-REVERT trial. ECHO, echocardiography; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction.

A total of approximately 280 patients will be randomly assigned to the three treatment groups in a 1:1:1 ratio, with approximately 90 patients per group including potential drop-outs. Patients will receive three doses of either 5 mg/kg or10 mg/kg of CDR132L or placebo on study day 1 (up to 18 days after the index MI event), day 29, and day 57. The study drug will be administered as short-term IV infusion on top of SoC treatment. All patients will be followed for efficacy and safety assessments up to study end at month 12. A first read-out of efficacy data will be performed after the double-blind period at month 6. *Figure 2* summarize the design of the study.

Study objectives and rationale for endpoints

The *Graphical Abstract* and *Table 1* summarize the main objectives and endpoints.

The principal objective of this trial is to study the safety and efficacy of two dose levels of CDR132L compared with placebo in post-MI patients with LV systolic dysfunction. The primary endpoint for this study will be the percent change from baseline in LV end-systolic volume index (LVESVI) at month 6. For quality assurance, data integrity and robustness, the imaging workflow has been detailed in an Imaging Study Manual, as part of the study protocol. Echocardiography is performed by specifically trained personnel. The echocardiography results are read and interpreted for the study purposes centrally (Echo Core Lab, Harvard Medical School). The assessing echo-reader is blinded to the study treatment assignments.

Main secondary objectives are safety and effects on cardiac function. Safety endpoints are the frequency of adverse events and abnormalities in clinical laboratory assessments, vital signs, physical examination, ECGs. Main efficacy endpoints include LVEF change from baseline at month 3, 6, and 12, absolute and relative LVESVI change from baseline at month 3, 6 and 12, and absolute LVESVI change from baseline at month 6, as well as troponin T, NT-proBNP change from baseline at months 3, 6 and 12. Well-being will also be evaluated by means of the Kansas City Cardiomyopathy Questionnaire (score and mean scores of subdomains symptom burden, physical limitation, and quality of life) change from baseline at months 6 and 12.

Exploratory endpoints related to efficacy include determining the effects of CDR132L on HF episodes, as time to first event for cardiovascular mortality, hospitalization or emergency department visit for HF conditions. It will also be evaluated on the change of disease score (NYHA class) and cardiac parameters by echocardiography (early and late diastolic transmitral flow velocity, early diastolic mitral annular velocity, left atrial volume index, systolic ejection time, and strain analysis for global longitudinal strain). We also plan to determine the effects of CDR132L on exploratory PD and target engagement biomarkers (e.g. cardiac fibrosis markers, and relevant circulating RNAs).

Data monitoring, interim analysis

A Data Safety Monitoring Board closely and continuously supervises all data to monitor the safety of all patients. No interim analysis for efficacy is planned. Primary analysis will be done once the last patient has completed the double-blind 6-month observation period. Follow-up data will be analysed in addition once the last patient has completed the last visit (month 12).

Statistical considerations

Sample size

The objective of the study is to determine the superiority of CDR132L versus placebo in reducing LVESVI. We estimate that a sample size of 90 in each group (270 in total) will have a 96.0% power to detect a difference in means of 5.0% (10 mg/kg CDR132L dose vs. placebo) assuming that the common standard deviation is 9 using a two-group *t*-test with a 2.5% one-sided significance level. Comparing the dose of 5 mg/kg CDR132L versus placebo, the sample size of 90 in each group will have 84.3% power to detect a difference in means of 4.0% using the same assumptions as above. Ten additional patients will be included to compensate for early drop-outs. It is planned that approximately 280 patients will be enrolled/randomized into the study in a 1:1:1 ratio.

Statistical methodology

The primary analysis population will be the intention-to-treat (ITT) population. Additional sensitivity analysis will also be done using the full analysis set.

Efficacy of CDR132L will be established by calculating the mean difference in change from baseline in percent change in LVESVI at month 6 among MI patients randomized to either active treatment or placebo group calculated in the ITT analysis set using analysis of covariance (ANCOVA). This primary analysis of the primary efficacy endpoint will be conducted regardless of intercurrent events. The change from baseline in continuous secondary endpoints will also be analysed using ANCOVA, with placebo acting as the reference. The model will include treatment as a fixed effect and baseline value as a covariate. In addition, safety analyses will also be conducted. However, no formal statistical analysis of the safety data will be performed. Subgroup analyses for the primary and selected secondary outcome parameters will be performed, including HF medication, age and LV function at baseline. A detailed statistical analysis plan including pre-specified subgroup analyses will be finalized ahead of database lock.

Discussion

Study rationale

This Phase 2 study aims to assess the efficacy and safety of CDR132L at 5 mg/kg and 10 mg/kg, given as three single IV doses administered 28 days apart as an add-on to SoC therapy, in a larger cohort of patients with HF and reduced LVEF after MI.

The current acute therapy after MI is early revascularization to restore myocardial perfusion and prevent necrosis. The long-term medical strategy after MI focuses on neurohormonal blockade. Indeed, early initiation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers,[24] the use of mineralocorticoid receptor antagonists[25] and beta-blockers is associated with improved mortality in MI patients.[9]

As opposed to the recently demonstrated proven benefit of SGLT2 inhibitors and angiotensin receptor–neprilysin inhibitor in HF with reduced LVEF,[26,27] no new drug has demonstrated long-term improvement in outcomes in the post-MI segment of HF patients.

Drug and dose rationale

Inhibition of miR-132 effectively prevents progression of HF in an animal model of post-MI HF.[20] Translational *in vitro* and *in vivo* studies have demonstrated the safety, tolerability, and efficacy of CDR132L in various forms of HF, paving the way for clinical development.[18,19] CDR132L's non-clinical data formed the basis of the Phase 1b study in 28 patients with stable HF (NYHA class I to III) of ischaemic origin.[22] The dose levels, ranging between 0.32 and 10 mg/kg of CDR132L administered IV twice were found to be well tolerated with minimal treatment-related or treatment-emergent adverse events. There were no notable, treatment-related, or clinically significant changes in liver function, renal function, or other laboratory results, vital signs, or physical examinations in any of the patient in either CDR132L or placebo group. PK analysis supported the good safety profile, with no accumulation, in line with a short plasma half-life of around 4 h, a restricted volume of distribution, and a high degree of dose linearity with regard to maximum plasma concentration.[22] In cardiac tissue of large animals CDR132L has a long half-life of several weeks, evident by long lasting reductions in functional and circulating miR-132 levels and by the therapeutic effects.[18,19] In humans, target engagement of CDR132L demonstrated a potent, dose-dependent and long lasting reduction of circulating miR-132 levels in plasma. CDR132L administration at dose levels >1 mg/kg achieved rapid and sustained reduction in plasma miR-132 over the 4-month course of the study. This was confirmed in a PK/PD modelling approach to guide dose selection in subsequent clinical studies.[22]

Based on the PK/PD modelling and safety considerations from non-clinical and the Phase 1b studies, 5 and 10 mg/kg were selected as the dose levels for this Phase 2 study. Pre-clinical assessment of CDR132L in large animal models demonstrated clinically relevant improvement in cardiac function at the proposed dose level. CDR132L tissue concentrations positively correlated with improvement of cardiac function.[18,19] Assessment of CDR132L PK characteristics in humans, compared with the large animal pig model, confirmed a high level of inter-species consistency with no signs for drug accumulation.[22] Due to the lack of accumulation in the Phase 1b study, it is anticipated that the highest dose of 10 mg/kg to be administered in the Phase 2 study will result in exposure levels that are comparable to those noted in the Phase 1b trial. Note that the non-clinical model showed beneficial effects with three monthly doses with no safety signals.[19] Thus, three single IV doses of CDR132L, 28 days apart from each other, were chosen to prolong the therapeutic effect by an additional month of CDR132L cardiac tissue exposure and to ensure that patients are not underdosed.

Based on safety, PK and PD data, a 10-month additional follow-up after the last dosing will be implemented to provide an adequate time window for evaluating safety of CDR132L at the selected doses of 5 mg/kg and 10 mg/kg.

Choice of endpoints

In the HF REVERT study, CDR132L is tested in patients with HF and reduced LVEF (≤45%) after MI. Patient selection for this Phase 2 trial is based on the robust effect observed in relevant pre-clinical studies in post-MI HF. However, given the clear evidence that CDR132L treatment provides persistent and clinically relevant therapeutic effects on cardiac function due to the anti-remodelling mode of action of CDR132L, it is expected that CDR132L will be beneficial in a broad range of HF conditions.[18–20]

The primary endpoint for the HF-REVERT trial is the change of LVESVI, from baseline to 6 months. The use of HF surrogate markers in early clinical development that correlate with hard outcome measures in late-stage clinical development is a major accelerator of clinical development. The quantitative relationship between short-term trial-level therapeutic effects on cardiac remodelling and long-term hard endpoints such as hospitalization and death has been clearly demonstrated in many trials.[28] Reverse remodelling is defined as a reduction in LV volume and wall stress leading to improvement of LV function. Reductions of LV end-systolic

volume are an established marker of reverse remodelling in HF, as successfully demonstrated for renin–angiotensin system inhibitors, beta-blockers, device-related therapies[28] or for sacubitril/valsartan.[29] A similar effect was demonstrated for CDR132L in a large animal model of chronic HF.[19] Thus, the expected positive change in LVESVI in this Phase 2 will likely translate into meaningful clinical benefit in future stages of clinical development.

Conclusion

HF-REVERT will determine whether CDR132L, an antisense miR-132 inhibitor, compared with placebo, improves cardiac functions and quality of life in patients with HF after MI. The HF-REVERT trial is the first trial to test an ASO inhibitor in HF patients after MI. The design of HF-REVERT considers the collective experience from prior trials in a patient population with a great unmet medical need. Results will provide the rationale for the conduct of a subsequent outcome trial to test the effect of CDR132L in HF patients.

Funding

The HF-REVERT study was funded by Cardior Pharmaceuticals GmbH.

Conflict of interest: J.B. received honoraria/consulting fees not related to this article from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Corvia, CVRx, Edwards, Novartis, Norgine, Pfizer, Roche, Vifor, and institutional research support from Abiomed, CVRx, Norgine, Roche, Zoll. S.D.S. is member of the advisory board of Cardior, reports consulting fees during the conduct of the study from Cardior and consulting fees outside the submitted work from Abbott, Action, Akros, Alnylam, American Regent, Amgen, Arena, Anacardio, AstraZeneca, Bayer, Bohringer-Ingelheim, BMS, Cardiac Dimensions, Cardior, Cardurion, CellProThera, Corvia, Cytokinetics, Daiichi-Sankyo, Dinaqor, GSK, Janssen, Lexicon, Lilly, Merck, Moderna, Myokardia, Novartis, Quantum Genomics, Roche, Sanofi-Pasteur, Sarepta, Tenaya, Theracos, Tremeau, Valo, received institutional grant support from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI. S.D.A. received honoraria/consulting fees from Amgen, Astra Zeneca, Actimed Therapeutics, Bioventrix, Brahms, Cordio, CVRx, Cytokinetics, Edwards, Faraday Pharmaceuticals, GSK, HeartKinetics, Novartis, Novo Nordisk, Repairon, Sanofi, Sensible Medical, Vectorious; and institutional research support from Abbott, Vifor; and has leadership and trial steering committee role at Abbott, Bayer, Boehringer Ingelheim, Cardior, Cardiac Dimensions, Impulse Dynamics, Occlutech, Pfizer, Servier, V-Wave. I.A.M. received honoraria/consulting fees not related to this article from AstraZeneca, Bayer, Cardior, Novartis, and Vifor. S.B., J.V. and S.R. are fulltime employees of Cardior Pharmaceuticals GmbH. G.F. reports consulting fees during the conduct of the study from Cardior, received honoraria/consulting fees from Bayer, Boehringer Ingelheim committee and trial steering committee role Amgen, Bayer, Boehringer Ingelheim, Impulse Dynamics, Medtronic, Novartis, Servier, Vifor. U.G. is board member of Cardior, reports consulting fees during the conduct of the study from Cardior. P.P. received honoraria/consulting fees and grand support outside this manuscript from Berlin Chemie, AbbottVascular, BMS, Merck, Renal Guard Solution, Impulse Dynamics, Cibiem, Bayer, Novartis, Servier, Boehringer Ingelheim, Amgen, Vifor, AstraZeneca. R.A.d.B.'s institution has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Novo Nordisk, and Roche; R.A.d.B. has had speaker engagements with and/or received fees from and/or served on an advisory board for Abbott, AstraZeneca, Bristol Myers Squibb, Cardior Pharmaceuticals GmbH, NovoNordisk, and Roche, and received travel support from Abbott, Cardior Cardior Pharmaceuticals GmbH, and NovoNordisk. O.V. is member of the advisory board of Cardior, reports consulting fees from Cardior, Cytokinetics; and institutional research support from AstraZeneca, Bayer, Cardurion. W.H. reports consulting fees during the conduct of the study from Cardior. T.T. received honoraria/consulting/advisory fee from Amicus Therapeutics AstraZeneca, Bayer, Boehringer Ingelheim, Sanofi-Aventis and Novo Nordisk, not related to this article. S.B. and T.T. are co-founders and shareholders, S.B. and T.T. filed and licensed patents regarding miR-132 through the Hannover Medical School to Cardior Pharmaceuticals GmbH.

Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

References

1. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J* 2020;**5**:15. https://doi.org/10.21037/amj.2020.03.03
2. Velazquez EJ, Francis GS, Armstrong PW, Aylward PE, Diaz R, O'Connor CM, *et al.*; VALIANT registry. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: The VALIANT registry. *Eur Heart J* 2004;**25**:1911–1919. https://doi.org/10.1016/j.ehj.2004.08.006
3. Solomon SD, Zelenkofske S, McMurray JJV, Finn PV, Velazquez E, Ertl G, *et al.*; Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;**352**:2581–2588. https://doi.org/10.1056/NEJMoa043938
4. Bahit MC, Kochar A, Granger CB. Post-myocardial infarction heart failure. *JACC Heart Fail* 2018;**6**:179–186. https://doi.org/10.1016/j.jchf.2017.09.015
5. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, *et al.*; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–2353. https://doi.org/10.1001/archinte.163.19.2345
6. Swaroop G. Post-myocardial infarction heart failure: A review on management of drug therapies. *Cureus* 2022;**14**:e25745. https://doi.org/10.7759/cureus.25745
7. Hellermann JP, Jacobsen SJ, Gersh BJ, Rodeheffer RJ, Reeder GS, Roger VL. Heart failure after myocardial infarction: A review. *Am J Med* 2002;**113**:324–330. https://doi.org/10.1016/S0002-9343(02)01185-3
8. Caffrey M. RECORD-MI: Real-World Study Highlights Risk of HF After a Heart Attack. Am J Manag Care [Internet]. 2023 Aug [cited 2024 Jan 18]. Available from: https://www.ajmc.com/view/record-mi-real-world-study-highlights-risk-of-hf-after-a-heart-attack
9. Frantz S, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J. Left ventricular remodelling post-myocardial infarction: Pathophysiology, imaging, and novel therapies. *Eur Heart J* 2022;**43**:2549–2561. https://doi.org/10.1093/eurheartj/ehac223
10. Kim GH, Uriel N, Burkhoff D. Reverse remodelling and myocardial recovery in heart failure. *Nat Rev Cardiol* 2018;**15**:83–96. https://doi.org/10.1038/nrcardio.2017.139
11. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L, Maggioni AP, *et al.*; PARADISE-MI Investigators and Committees. Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. *N Engl J Med* 2021;**385**:1845–1855. https://doi.org/10.1056/NEJMoa2104508
12. Montalescot G, Alexander JH, Cequier-Fillat A, Solomon SD, Redheuil A, Hudec M, *et al.* Firibastat versus ramipril after acute mechanical reperfusion of anterior myocardial infarction: A phase 2 study. *Am J Cardiovasc Drugs* 2023;**23**:207–217. https://doi.org/10.1007/S40256-023-00567-8
13. von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M, *et al.* Empagliflozin in acute myocardial infarction: The EMMY trial. *Eur Heart J* 2022;**43**:4421–4432. https://doi.org/10.1093/eurheartj/ehac494
14. US National Library of Medicine. Dapagliflozin Effects on Cardiometabolic Outcomes in Patients With an Acute Heart Attack. (DAPA-MI). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04564742

15. US National Library of Medicine. EMPACT-MI: A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack (Myocardial Infarction). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04509674
16. James S, Erlinge D, Storey RF, Mcguire DK, De Belder M, Cantab BA, *et al.*; DAPA-MI Investigators. Dapagliflozin in myocardial infarction without diabetes or heart failure. *NEJM Evid* 2023. https://doi.org/10.1056/EVIDoa2300286
17. Ucar A, Gupta SK, Fiedler J, Erikci E, Kardasinski M, Batkai S, *et al.* The miRNA-212/132 family regulates both cardiac hypertrophy and cardiomyocyte autophagy. *Nat Commun* 2012;**3**:1078. https://doi.org/10.1038/ncomms2090
18. Foinquinos A, Batkai S, Genschel C, Viereck J, Rump S, Gyöngyösi M, *et al.* Preclinical development of a miR-132 inhibitor for heart failure treatment. *Nat Commun* 2020;**11**:633. https://doi.org/10.1038/s41467-020-14349-2
19. Batkai S, Genschel C, Viereck J, Rump S, Bär C, Borchert T, *et al.* CDR132L improves systolic and diastolic function in a large animal model of chronic heart failure. *Eur Heart J* 2021;**42**:192–201. https://doi.org/10.1093/eurheartj/ehaa791
20. Hinkel R, Batkai S, Bähr A, Bozoglu T, Straub S, Borchert T, *et al.* AntimiR-132 attenuates myocardial hypertrophy in an animal model of percutaneous aortic constriction. *J Am Coll Cardiol* 2021;**77**:2923–2935. https://doi.org/10.1016/j.jacc.2021.04.028
21. Huang C-K, Kafert-Kasting S, Thum T. Preclinical and clinical development of noncoding RNA therapeutics for cardiovascular disease. *Circ Res* 2020;**126**:663–678. https://doi.org/10.1161/CIRCRESAHA.119.315856
22. Täubel J, Hauke W, Rump S, Viereck J, Batkai S, Poetzsch J, *et al.* Novel antisense therapy targeting microRNA-132 in patients with heart failure: Results of a first-in-human phase 1b randomised, double-blind, placebo-controlled study. *Eur Heart J* 2021;**42**:178–188. https://doi.org/10.1093/eurheartj/ehaa898
23. US National Library of Medicine. Study to Assess Efficacy and Safety of CDR132L in Patients With Reduced Left Ventricular Ejection Fraction After Myocardial Infarction (HF-REVERT). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05350969
24. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, *et al.*; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906. https://doi.org/10.1056/NEJMoa032292
25. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.*; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321. https://doi.org/10.1056/NEJMoa030207
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
27. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:e263–e421. https://doi.org/10.1016/j.jacc.2021.12.012
28. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: A meta-analytic approach. *J Am Coll Cardiol* 2010;**56**:392–406. https://doi.org/10.1016/j.jacc.2010.05.011
29. Januzzi JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, *et al.*; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019;**322**:1085–1095. https://doi.org/10.1001/jama.2019.12821