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 (<= 45%) After Myocardial Infarction (HF-REVERT)

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This study has been transitioned to CTIS with ID 2023-507569-24-00 check the CTIS register for the current data. This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess theefficacy and safety of CDR132L in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON53818

Source
ToetsingOnline

Brief title
CDR132L (Cardior)

Condition

- Heart failures

Synonym
Reduced Left Ventricular Ejection Fraction

Research involving

Human

Sponsors and support

Primary sponsor: IQVIA Biotech
Source(s) of monetary or material Support: cardior pharmaceuticals Inc.

Intervention

Keyword: Ejection Fraction, HF-REVERT

Outcome measures

Primary outcome

The primary endpoint is defined as percent (%) change from baseline LVESVI at

Month 6

compared with baseline (after reperfusion, before treatment start) on top of

SoC as measured by

ECHO (central laboratory).

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 (μT10) and the 5

mg/kg dose group

(μT5) in comparison to placebo (μP) within a hierarchical test procedure with 2

steps:

Step 1

• H01: μT10 <= μP

• H11: μT10 > μP

If Step 1 is successful, then proceed to Step 2.

CONFIDENTIAL Protocol CDR132L-P2-01 - original protocol

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

Step 2

• H02: μT5 <= μP

• H12: μT5 > μP

To show superiority, the effect of the 10 mg dose group on the percent change in LVESVI must be larger (i.e., higher decrease) than the effect within the placebo group.

The percent change from baseline in LVESVI will be analyzed using ANCOVA, with placebo acting as the reference. The model will include treatment as a fixed effect and baseline LVESVI as a covariate.

Secondary outcome

The change from baseline in continuous secondary endpoints will also be analyzed using ANCOVA, with placebo acting as the reference. The model will include treatment as a fixed effect and baseline value as a covariate.

Study description

Background summary

Current state-of-the-art HF pharmacotherapy is largely focused on symptomatic management;
that is, mainly on reducing cardiac load by reducing neurohormonal overdrive and volume
retention. 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.14 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 reduce the financial burden of HF care.
The mechanism of action (MoA) of CDR132L has the following key elements forming the basis
of its role as a novel drug in HF: a) normalization of aberrant cardiac miR-132 levels, b)
normalization of calcium signaling and contractility as well as cardiac function, c) improvement
in cardiac autophagy and homeostasis, and d) attenuation of maladaptive cardiac remodeling
(reducing pathological cardiomyocyte growth and cardiac fibrosis)

Study objective

This study has been transitioned to CTIS with ID 2023-507569-24-00 check the CTIS register for the current data.

This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess the
efficacy and safety of CDR132L in patients with reduced LVEF (<= 45%) after MI.

Primary:
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 patients with reduced LVEF <= 45% after MI (STEMI or NSTEMI) as add-on therapy to SoC treatment

Secondary:
- 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 patient well-being

Exploratory:
- To determine the effects of CDR132L compared with placebo on HF episodes
- To determine the effects of CDR132L compared with placebo on cardiac parameters
- To determine the effects of CDR132L compared with placebo on exploratory biomarkers and immunogenicity

Study design

This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess
efficacy and safety of CDR132L in patients with reduced LVEF (<= 45%) after MI. As shown in
Figure 1, 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.
Patients will be screened to determine eligibility at least 3 days after MI diagnosis; all eligibility
criteria must be confirmed no later than 14 days after MI diagnosis. Screening and dosing can be
done in an inpatient (in case patients are hospitalized due to MI or HF) or outpatient setting. A
total of approximately 280 unique individual patients will be randomly assigned to the
3 treatment groups in 1:1:1 ratio, with approximately 90 patients in each treatment group. Groups
1 and 2 will include patients who will receive CDR132L 5 mg/kg or 10 mg/kg, respectively.
Patients in the placebo group (Group 3) are included for evaluation of efficacy and safety.
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.
All patients will be required to attend the study visits as described in the Schedule of Activities
(SoA; Section 1.3). All patients will receive SoC therapy post MI and eventually for HF.
CDR132L or placebo will be administered as add-on therapy to the SoC treatment. All patients
will be followed for 10 months for efficacy and safety assessments. Overall, study duration for
each patient will be approximately 12 months.
A Data Safety Monitoring Board (DSMB) will closely supervise all data to monitor the safety of
all patients. The DSMB Charter will describe the membership, roles, responsibilities, and
operating guidelines of the DSMB.
Approximately 60 European study centers will be selected according to their expertise in
performing complex, early phase clinical studies as well as their ability to follow guidelines on
established SoC treatment of post MI and HF patients. The study centers must have sufficiently
trained study personnel to guarantee adherence to this study protocol.

Intervention

-Group 1 receives 5 mg/kg of study drug.
-Group 2 receives 10 mg/kg of the study drug.
-Group 3 gets the placebo.

Study burden and risks

The global burden of HF is significant, with an estimated prevalence of 64.34 million cases
contributing to 9.91 million years lost to disability. Heart failure complicating acute MI is
common and is a powerful predictor of death. The incidence of HF among patients hospitalized
for MI varies between 14% and 36%. Inhibition of miR-132 effectively prevents progression
of HF in an animal model of the disease, and translational in vitro and in vivo studies have
demonstrated the safety, tolerability, and efficacy of CDR132L in HF. In

addition, a recent
first-in-human (FIH) study exploring a range of doses (0.32 to 10 mg/kg)
reported CDR132L to
be safe and well tolerated in patients with stable ischemic HF as an add-on
therapy to Standard
of Care (SoC), and supports the progression to the next stage of clinical
development.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female of non-childbearing potential patients, aged >= 30 to <= 80
years at the date of signing informed consent which is defined as the beginning
of the Screening Period.

2. Spontaneous AMI (type I) based on the universal MI definition with randomization to occur no later than 14 days after index event diagnosis.
3. Patient with a LVEF <= 45% as measured by ECHO after MI diagnosis (STEMI or NSTEMI).
4. Patient with NSTEMI with evidence of significant myocardial necrosis, evidenced through a troponin T or troponin I increase to at least 5 times the upper limit of normal (ULN) at MI index event diagnosis.
5. Patient with previous MI events in history can be included.
6. A male patient must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 30 days after the last dose of study treatment and refrain from donating sperm during this period.
7. Patient with body weight of <= 120 kg.
8. N-terminal pro B-type natriuretic peptide level >= 125 pg/ml and < 8000 pg/ml. Note: 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).
9. Patient with STEMI/NSTEMI who underwent percutaneous coronary intervention or angiography (if no indication for stent placement or balloon procedure) for this event.
10. Capable of giving signed informed consent as described in Appendix 2 of the protocol, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

1.A woman of childbearing potential (WOCBP) as defined in Appendix 5. 2.Patient with HF of non-ischemic origin; e.g., myocarditis, alcoholic cardiomyopathy. 3.Patient with history of decompensated HF or a history of LVEF <30% within 6 months prior to MI Index event. 4.Patient with NYHA class IV at screening or randomization. 5.Patient has any planned cardiac intervention (angiogram without angioplasty is acceptable) or any other planned surgery after the Screening Period. 6.Patient has severe valvular heart disease. 7.Patient has systolic BP < 90 mmHg or > 180 mmHg, diastolic BP < 50 mmHg or > 110 mmHg, and/or heart rate < 50 or > 100 beats/minute at screening or randomization. 8.Patient with an estimated glomerular filtration rate < 30 mL/min/1.73 m2 or on dialysis. 9.Patient with hepatic insufficiency classified as Child Pugh B or C. 10.Patient with known active human immunodeficiency virus, Hepatitis B, or Hepatitis C infection at screening. 11.Impaired hepatic function defined by a total bilirubin level of >= 2 × the ULN and ALT levels of >= 3 × ULN. 12.Patient has medical history of disease(s) affecting the blood-brain-barrier, e.g., stroke within 6 months or multiple sclerosis. 13.Patient has medical history of bleeding disorders or has thrombocytopenia (platelets < 100,000/µL). 14.Patient

has poorly controlled diabetes as determined by the Investigator. 15.Patient is currently on treatment for epilepsy. 16.Patient has a 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. 17.Patient has a 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. 18.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. This will include patients with any of the following (at Screening Visit or Day -1): a)Clinically significant PR (PQ) interval prolongation. b)Intermittent second- or third degree atrioventricular block. c)Sustained cardiac arrhythmia including (but not limited to) supraventricular tachycardia, any symptomatic arrhythmia with the exception of isolated extra systoles. 19.Patient with active and clinical-relevant *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)* infection confirmed as per the local testing guidelines at screening. 20.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. 21.Patient has received an investigational product or treated with an investigational device within 90 days prior to first study drug administration. 22.Patient has known or suspected intolerance or hypersensitivity to the study drug, any closely related compound, or any of the stated ingredients. 23.Patient is not to be enrolled into the study if they received any prohibited therapy within 3 months before the first administration of study drug. a)Treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapy, or gene therapy) at any time during the study. b)Administration of any other investigational agent within 3 months before the first administration of study drug or at any time before the patient*s completion of the study. 24.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).

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-07-2022
Enrollment:	38
Type:	Actual

Ethics review

Approved WMO Date:	15-03-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-06-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	28-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-507569-24-00
EudraCT	EUCTR2021-006040-27-NL
ClinicalTrials.gov	NCT04045405
CCMO	NL80128.042.22