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Phase I study to evaluate the safety of mRNA-0184 in participants with heart failure

Submission date
28/05/2022

Recruitment status
No longer recruiting

Registration date
21/10/2022

Overall study status
Completed

Last Edited
01/11/2022

Condition category
Circulatory System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Chronic heart failure (HF) is a condition commonly caused by an abnormality or damage to the heart muscle. Approximately 920,000 people in the UK have been diagnosed with HF. The goals of treatment are to improve the patient's quality of life and reduce mortality. mRNA-0184 is an investigational drug that is being studied to determine its ability to increase your body's ability to make a protein like a naturally occurring hormone called relaxin, which promotes the widening of blood vessels and the formation of new blood vessels. The aim of this study is to evaluate the safety and tolerability of single and multiple doses of mRNA-0184 in participants with chronic HF.

Who can participate?
Patients aged 18 years and over with HF

What does the study involve?
The study has a single ascending dose (SAD) and a multiple ascending dose (MAD) stage. Each stage will be split into several groups based on the dose of mRNA-0184 that will be given. Participants in the SAD groups will receive one dose of mRNA-0184 and are expected to be in the study for up to 31 weeks. Participants enrolled in the MAD groups will be assigned by chance in a 3:1 ratio to receive up to 4 doses of either mRNA-0184 or placebo (an inactive substance that looks like the study drug). Treatment will be administered at dosing intervals of once every 2, 3 or 4 weeks, depending on data from the SAD groups. The duration for participants in these groups is up to 46 weeks depending on the dosing interval. All participants will be closely monitored during the study drug infusion and for a period after completion of the infusion. Study procedures include physical examinations, blood and urine samples, questionnaires, ECGs, ultrasounds of the heart and kidneys and monitoring of blood pressure and heart rate/rhythm.

What are the possible benefits and risks of participating?
As part of being in this study, the participant's condition will be closely monitored by doctors who specialise in heart health (cardiologists). The study drug is intended to increase the body's ability to make a protein similar to a naturally occurring hormone called relaxin. Researchers believe that increasing the amount of relaxin in the body will reduce symptoms of heart failure. Participants could see an improvement in their heart failure symptoms; however, there is no

guarantee there will be any benefits from their taking part in this clinical study. In addition, this study may improve both their understanding and the healthcare field's understanding of heart failure and how it responds to the study drug. Participating in this study may help people with heart failure in the future.
This is a Phase I first-in-human study where the study drug has not been tested in humans previously and therefore there is little information on the possible risks and adverse reactions associated with the IV administration of mRNA 0184. There may be side effects and discomforts from the study drug that are not yet known. The study doctor will discuss all information regarding possible side effects of the study drug with participants.
There is a small chance that the participant will experience an infusion-related reaction/allergic reaction to mRNA-0184. Infusion-related reactions (IRRs)/allergic reactions may range from mild, such as skin rash or hives, to severe such as breathing difficulties or shock. A severe reaction would require immediate medical treatment and could result in permanent disability or death. Participants in the Single Ascending Dose (SAD) cohort will be closely monitored in the hospital for at least 24 hours after receiving the study drug, and participants in the Multiple Ascending Dose (MAD) cohort will be monitored for at least 6 hours after the first infusion of study drug and for at least 4 hours after the study drug infusion on subsequent doses, to ensure the participants' safety. To prevent or reduce the severity of any IRRs, participants will receive several medications (acetaminophen/paracetamol, H1-receptor blocker and H2-receptor blocker) about 60 minutes before infusion of the study drug. The study team administering the study drug have experience in administering IV infusions and are trained to know what to do in the event of a serious reaction. Participants will be told about any new findings that develop during the course of the study, which may affect their decision to stay in the study.
There may be a possibility that the study drug could damage an unborn child or nursing infant. Therefore, patients that are pregnant, planning to become pregnant or breastfeeding must not enter this study. From screening, throughout the duration of the study and for 6 months after the last infusion of the study drug, women of childbearing potential and sexually active males must use an adequate method of contraception. This will be fully explained in the participant information sheet.
Participants will need to schedule time out of their normal routine to attend extra clinic visits. As the study drug infusions can take up to 4 hours to administer and close monitoring of the patient is needed for 24 hours after infusion of the study drug in the SAD cohort and for 6 hours after infusion of the study drug in the MAD cohort, the participant may need to stay in the hospital for extended periods of time or overnight. Participants will also need to take a blood pressure measurement at least once a day for up to 17 weeks depending on whether they are in the SAD or MAD cohort. Participants will also be asked to wear an ambulatory blood pressure monitor (ABPM) and a Holter monitor for at least 24 hours up to 6 times during the study. Due to the amount of time the participant will need to spend in clinic visits and the burden of daily blood pressure monitoring and wearing monitoring equipment, participants will receive specified patient stipends as compensation for their time. Reasonable travel expenses for study clinic visits will also be reimbursed.
Taking blood may cause some discomfort, bruising and, very rarely, infection where the needle goes into the skin. The patient may also experience dizziness, nausea, or fainting during blood collections. Ambulatory blood pressure monitoring (ABPM) is virtually free of risk, except for a small chance of skin irritation where the cuff is applied. Some other discomforts that have been reported are that the device is noisy, that wearing the device can cause some inconvenience to normal daily routine, and disturbances to sleep. The ECG is a safe procedure with no known risks. Some people may be allergic or sensitive to the sticky patches used to attach the electrodes. This can cause skin irritation, itching and redness. Removing the sticky patches can feel like having an adhesive bandage taken off. The Holter monitor is virtually free of risk, except for a small chance of skin irritation at the site of electrode placement similar to the ECG.

Where is the study run from?
Moderna (France)

When is the study starting and how long is it expected to run for?
May 2022 to July 2024

Who is funding the study?
Moderna (France)

Who is the main contact?
Prof. Chim Lang
c.c.lang@dundee.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Chim Lang

Contact details
Ninewells Hospital & Medical School
Dundee
United Kingdom
DD1 9SY
+44 (0)1382 383 283
c.c.lang@dundee.ac.uk

Type(s)
Public

Contact name
Prof Chim Lang

Contact details
Ninewells Hospital & Medical School
Dundee
United Kingdom
DD1 9SY
+44 (0)1382 383 283
c.c.lang@dundee.ac.uk

Type(s)
Principal investigator

Contact name
Prof Chim Lang

Contact details

Ninewells Hospital & Medical School
Dundee
United Kingdom
DD1 9SY
+44 (0)1382 383 283
c.c.lang@dundee.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2022-000784-46

Integrated Research Application System (IRAS)
1005671

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
mRNA-0184-P101, IRAS 1005671, CPMS 50852

Study information

Scientific Title
A Phase I, adaptive, open-label, single ascending dose to single-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of mRNA-0184 in participants with chronic heart failure

Study objectives
1. Evaluate the safety and tolerability of single and multiple doses at escalating dose levels of intravenously (IV) administered mRNA-0184
2. Characterize the pharmacokinetic (PK) profile of mRNA encoding relaxin-2-variable light chain kappa (Rel2-vlk mRNA) and of SM-86/OL-56 following single and multiple dose administration at escalating dose levels of mRNA-0184
3. Characterize the pharmacodynamic (PD) response of single and multiple dose administration at escalating dose levels of mRNA-0184
4. Assess the presence and development of anti-polyethylene glycol (anti-PEG) antibodies and anti–Rel2-vlk protein antibodies

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/10/2022, South Central – Oxford A REC (Temple Quay House, 2 The Square, Bristol Research Ethics Committee Centre, BS1 6PN, UK; +44 207 104 8206; oxforda.rec@hra.nhs.uk), ref: 22/SC/0208

Study design
Open-label single ascending dose to single-blind randomized placebo-controlled multiple ascending dose trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic heart failure

Interventions
The study has a Single Ascending Dose (SAD) and a Multiple Ascending Dose (MAD) stage. Each stage will be split into several groups based on the dose of mRNA-0184 that will be given.

In the SAD stage, participants will be given a single dose of mRNA-0184 and will be followed for safety for 26 weeks after dosing. The SAD stage includes five dose cohorts with the option of two additional cohorts, for a maximum of seven cohorts. The initial dose will be 0.025 mg/kg and the dose in subsequent cohorts will not exceed the proposed maximum dose of 1.0 mg/kg. Dosing will follow a “3+3” design; each cohort in the SAD stage includes a minimum of three sentinel participants who will each receive a single IV infusion of mRNA-0184. Each sentinel participant will be monitored for safety for a minimum of 7 days before the next sentinel participant is dosed. Participants will be closely monitored for safety in the clinic for at least 24 hours after completion of the infusion. If one of the participants in a given cohort meets dose-limiting toxicity criteria within 7 days after the dose, an additional three participants may be enrolled in that cohort to further characterise the safety and tolerability of that dose. If a second dose-limiting toxicity occurs within the cohort, the Safety Monitoring Committee will review and make a recommendation on how the study should proceed. The last participant in a SAD cohort will be monitored for safety for a minimum of 7 days before dosing participants in the next SAD dose level or before dosing participants in a MAD cohort at the same or lower dose level(s).

In the MAD stage, participants will receive up to four planned doses of mRNA-0184 or placebo via IV infusion and will be followed for safety for 26 weeks after the end of treatment visit. There will be a maximum of seven MAD cohorts. Within each cohort, eight participants will be randomised in a 3:1 ratio to mRNA-0184 or placebo. The dose levels will not exceed the highest dose cleared in any SAD cohort. The dosing regimen will be at prespecified intervals of once every 2, 3, or 4 weeks, with treatment occurring over 8 weeks, 12 weeks and 16 weeks, respectively. The selection of dosing interval will be determined based on data from the SAD stage. A sentinel dosing strategy will not be employed in the MAD cohorts. Participants will be closely monitored in the clinic for at least 6 hours after completion of the infusion for Dose 1 and observed for at least 4 hours in clinic after completion of the infusion on subsequent doses. Participants previously enrolled in a SAD cohort will be permitted to enroll into a MAD cohort after a washout period of at least 5 effective half-lives of the Rel2-vlk protein (as calculated from clinical data collected in the SAD cohort) or 45 days (if Rel2-vlk protein t1/2 cannot be estimated).

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
mRNA-0184

Primary outcome(s)
1. Incidence and severity of TEAEs, SAEs, and TEAEs leading to treatment discontinuation. This is measured at 26 weeks for the SAD stage, 8 weeks for the MAD stage Q2W, 12 weeks for the MAD stage Q3W and 16 weeks for the MAD stage Q4W.
2. Vital signs, weight, physical examination findings, ECG results, and laboratory findings (including hematology, serum chemistry, urinalysis, and coagulation parameters). This is measured at 26 weeks for the SAD stage, 8 weeks for the MAD stage Q2W, 12 weeks for the MAD stage Q3W and 16 weeks for the MAD stage Q4W.

Key secondary outcome(s))
1. PK of mRNA-0184 assessed as serum concentrations of Rel2-vlk mRNA and plasma concentrations of SM-86/OL-56. Parameters will include, but are not limited to, Cmax, Tmax, AUClast, AUC0-t, AUC0-∞, t½, CL/F, and Vz/F
2. PD of mRNA-0184 assessed as serum concentrations of Rel2-vlk protein. Parameters will include, but are not limited to, Emax, TEmax, AUEC, AUEC0-t, AUEC0-∞, and t½
3. Quantification of transthoracic echocardiography (TTE) PD markers. This will include, but not be limited to: stroke volume (SV), CO, cardiac index (CI), ejection fraction (EF), systemic vascular resistance (SVR), measures of left ventricular filling pressures and diastolic function, left ventricular strain, and pulmonary artery pressure.
4. Anti-PEG antibodies measured using ELISA ligand binding assay
5. Anti–Rel2-vlk protein antibodies measured using assay that has not been validated yet

These are measured at 26 weeks for the SAD stage, 8 weeks for the MAD stage Q2W, 12 weeks for the MAD stage Q3W and 16 weeks for the MAD stage Q4W.

Completion date
04/07/2024

Eligibility

Key inclusion criteria
1. Age ≥18 years at the time of informed consent
2. Documented diagnosis of HF based on medical records
3. Left ventricular ejection fraction (LVEF) ≥35% and <50% at Screening, or documented within the 3 months before Screening, measured by TTE or cardiac magnetic resonance imaging (MRI)
4. New York Heart Association (NYHA) HF Class I or II
5. On a stable regimen of cardiovascular medication(s) for a duration of at least 4 weeks before Screening
6. Heart rate ≥50 bpm at Screening
7. Systolic blood pressure ≥110 mmHg and ≤160 mmHg at Screening
8. Sexually active female participants of childbearing potential and sexually active male participants of reproductive potential agree to use a highly effective method of contraception during the study and for 6 months after the last administration of IP

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Hospitalized for cardiovascular causes within 3 months before Screening
2. Decompensated HF, acute myocarditis, hypertrophic and/or restrictive/constrictive cardiomyopathy, or moderate or severe valvular heart disease (as classified by echocardiography) at Screening or within the 3 months before Screening. Moderate tricuspid regurgitation is not exclusionary
3. Symptoms of angina pectoris at Screening
4. Severe obstructive or restrictive pulmonary pathology, including chronic obstructive pulmonary disease Gold Stage III or IV current use of oxygen therapy, or pulmonary hypertension
5. History of sustained ventricular tachycardia or atrial fibrillation/atrial flutter with a ventricular response ≥110 bpm at the time of Screening
6. Severe renal impairment defined as one or both of the following:
6.1. Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, calculated using the Simplified Modification of Diet in Renal Disease equation
6.2. Current or planned dialysis or ultrafiltration
7. Prolonged QTcF >450 ms at Screening
8. Laboratory abnormality within an exclusionary threshold at Screening
9. For female participants, positive pregnancy test at Screening or Baseline or currently breastfeeding
10. Hypersensitivity to acetaminophen/paracetamol or H1-receptor or H2-receptor blockers
11. History of hypersensitivity to any components of the IP
12. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive hepatitis B surface antigen [HBsAg] result), hepatitis C virus (HCV), or HIV (positive HIV-1/HIV-2 antibodies). Participants with a past or resolved hepatitis virus B (HBV) infection(defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acids (RNA)
13. Participant has received a COVID-19 vaccination (irrespective of type of vaccine) or is anticipated to require a second dose of a two-dose COVID-19 vaccine series within 7 days of the planned date of IP administration
14. For SAD cohort participants to be rolled over into the MAD stage, have experienced a DLT in a SAD cohort
15. Participation in another clinical study of another IP within 30 days before Screening or within 5 effective elimination half-lives of the IP, whichever is longer
16. Has a positive urine drug screen for any of the following nonprescription drugs of abuse at Screening: alcohol, opiates, cocaine, phencyclidine, amphetamines, methamphetamines, barbiturates, benzodiazepines, or methadone. Positive drug screens for benzodiazepines or opiates will not be exclusionary if prescribed concomitant medications can justify the result
17. Any other clinically significant medical condition that, in the Investigator’s opinion, could

interfere with the interpretation of study results or limit the participant’s participation in the study

Date of first enrolment
26/09/2022

Date of final enrolment
15/08/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Ninewells Hospital
Ninewells Avenue
Dundee
United Kingdom
DD1 9SY

Study participating centre
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
Moderna France

Funder(s)

Funder type
Industry

Funder Name
Moderna

Alternative Name(s)
Moderna Therapeutics, Moderna, Inc., Moderna, Inc

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No