A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Effects of Multiple Subcutaneous Injections of Elamipretide on Left Ventricular Function in Subjects with Stable Heart Failure with Reduced Ejection Fraction

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Primary: To evaluate the effects of multiple subcutaneous (SC) doses of elamipretide on left ventricular end systolic volume (LV ESV) assessed by cardiac Magnetic Resonance Imaging (MRI)Secondary:* To evaluate the safety and tolerability of multiple...

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

Summary

ID

NL-OMON45900

Source
ToetsingOnline

Brief title
effect of multiple injections Elamipretide on chronic heart failure

Condition

- Heart failures

Synonym
Stable Heartfailure

Research involving
Human

Sponsors and support

Primary sponsor: Stealth BioTherapeutics Inc.
Source(s) of monetary or material Support: Pharmaceutical Company

Intervention

Keyword: elamipretide, left verntricular function, reduced ejection fraction, stable heart failure

Outcome measures

Primary outcome

Primary Endpoints

Change from baseline in left ventricular end systolic volume (LV ESV) assessed

by cardiac

MRI

Secondary outcome

Secondary Endpoints

** Adverse events (AEs)

** Changes from baseline in vital signs

** Changes from baseline in electrocardiograms (ECGs)

** Changes from baseline in clinical laboratory evaluations

** Changes from baseline in the following parameters assessed by cardiac MRI:

o LV EF

o LV end diastolic volume (EDV)

** Changes from baseline in the following parameters assessed by

echocardiography:

o E/A (ratio between early and late mitral inflow velocity),

o E/e* (Ratio between early mitral inflow velocity and mitral annular early

diastolic velocity)

o LV EDV, LV ESV and biplane EF

o LV global longitudinal strain

o LA volume

o LV mass

o Mitral regurgitation severity

o Tricuspid regurgitation severity

o RV fractional area change

o RV systolic pressure (RVSP)

Study description

Background summary

It is estimated that approximately 1-2% of the adult population in developed countries has Heart
Failure (HF) and the prevalence is rising to *10% among persons 70 years of age or older.
HF incidence is continuously increasing.

Despite the significant improvement in symptoms and survival observed with pharmacologic blockade of the renin-angiotensin and beta adrenergic sys-tems, such drug therapy generally has had limited impact on exercise capacity.

This has led to the concept that multi-targeted mechanistic approaches to HF are required to suc-cessfully translate experimental interventions into protection against the clinical manifestations of the disease state, as well as beneficially impacting its associated major adverse events, including recurrent hospitalization and death. Such a broad-based ap-proach must include therapies that simultaneously impact multiple affected organ systems and cellular mechanisms.

Elamipretide, with its multi-organ beneficial actions on function and metabolism in vitro and in animal models, is a promising candidate for targeting the complex interplay of factors that ultimately result in the syndrome of clinical HF. The potential of elami-pretide to treat the multiple organs systems and or-ganelles that contribute to the HF state represents an important opportunity to address a critical and unmet clinical need.

The study drug has been given as single intravenous (into a vein) dose in heart failure patients, but not as multiple subcutaneous doses. This will be the first study where the study drug is being given as multi-ple subcutaneous injections to patients with chronic heart failure.
Protocol page 15, section 4.1

Study objective

Primary:
To evaluate the effects of multiple subcutaneous (SC) doses of elamipretide on left ventricular end systolic volume (LV ESV) assessed by cardiac Magnetic Resonance Imaging (MRI)

Secondary:
* To evaluate the safety and tolerability of multiple SC doses of elamipretide
* To evaluate the effects of multiple SC doses of elamipretide on LV systolic and diastolic function, LV volumes, LV global longitudinal strain, left atrial (LA) volume, LV mass, mitral and tricuspid regurgitation severity, and right ventricular (RV) function

Exploratory:
To evaluate the effects of multiple SC doses of elamipretide on:
- 6-minute walking distance
- Quality of Life
- N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels
- Change in Borg dyspnea scale

Study design

A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study

Intervention

Elamipretide (MTP-131) will be supplied as 40 mg/1 mL of sterile solution for subcutaneous injection. The doses of elamipretide will be 4 mg or 40 mg administered as a once daily SC injection.

You will be randomly assigned to 1 of 3 treatment groups:
* Group 1 will receive a daily dose of placebo (a sterile solution of salt in

water, otherwise known as saline) for 28 days
* Group 2 will receive a daily dose of 4mg of study drug for 28 days
* Group 3 will receive a daily dose of 40mg of study drug for 28 days

Study burden and risks

- the amount and number of blood samples (seeE6, 11x) ,
- the number of site visits (8x),
- physical examinations or other tests: every visit, incl 3x times an MRI scan (once with contrast dye, and twice without)
- questionnaires (2 types),
- the risks associated with the investigational product:
Based on the clinical and non-clinical study data, accepatable safety risks are expected for the proposed current study. Visiting nurses will visit subjects daily to administer study medication and therefore subjects will have an opportunity to report any safety concerns on a daily basis.

Common side effects in the phase I study were:
Headache, nausea and low serum sodium values.

When the study drug was injected directly under the skin, the most commonly observed injection site reaction was mild erythema (redness) and/ or mild itchiness (pruritis), which generally occurred within 5 minutes of administration.

Patients with decreased renal function will have higher study drug blood levels after taking the drug. To dat, there have not been more side effect in patients with decreased kidney function compared to peaple with normal kidney function.

MRI scan:
Patients may be allergic to the contrast dye used for the initial MRI scan (screening visit), or experience claustrophobia during the scanning process.

Contacts

Public
Stealth BioTherapeutics Inc.

275 Grove Street suite 3-107
Newton, MA 02466
US
Scientific
Stealth BioTherapeutics Inc.

275 Grove Street suite 3-107
Newton, MA 02466
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any study-related procedures;
2. Age *40 and *80 years;
3. A known history of chronic ischemic or non-ischemic cardiomyopathy of at least 6 months duration from the time of the initial diagnosis, or signs and symptoms consistent with heart failure;
4. Receiving heart failure (HF) treatment, including, but not limited to, angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), and an evidence-based beta blocker for the treatment of HF. Subjects who cannot tolerate ACEI or ARB due to reduced renal function or hypotension are eligible. Subjects may be receiving aldosterone antagonists, but this is not a requirement for the study;
5. HF is considered to be stable in the judgment of the Investigator AND doses of HF treatment have been stable for at least 1 month prior to the Screening Visit;
6. In normal sinus rhythm (electrocardiogram documented) at Screening and Day 1 and no history of atrial fibrillation in the past 12 months;
7. No hospitalization related to HF within 1 month prior to the Screening Visit;
8. Left Ventricular Ejection Fraction (LVEF) * 40% by 2-D echocardiography at Screening;
9. At least 3 viable segments (hyperenhancement * 25%) by a qualifying delayed gadolinium-enhanced cardiac MRI examination at Screening (confirmed by independent core lab);
10. Willing to adhere to the study requirements for the length of the trial;
11. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study medication;
a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject

agrees to use an acceptable method of contraception should they become sexually active;
b. Maintenance of monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis);
c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system;;Note: Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit);

Exclusion criteria

1. History of any concurrent medical condition which, in the opinion of the Investigator, significantly increases the potential risks associated with administration of study medication or any other aspect of study participation;
2. Any contraindication to MRI scanning as assessed by local MRI safety questionnaire, which may include;
a. History of intra-orbital metal fragments which have not been removed;
b. Severe claustrophobia;
c. Non-MRI safe cochlear implant(s) or intracranial aneurysm clips;
d. Extensive tattoos located on the torso that contain metallic inks;
e. Other non-removable implanted metallic or electronic devices that have not been determined to be MRI safe;
f. Inability to lie flat;
3. Inadequate echocardiogram image quality (defined as poor sound transmission and/or < 10 endocardial segments seen);
4. LVEDD indexed to Body Surface Area is > 45 mm/m2 assessed by 2-D echocardiography;
5. Coronary or peripheral revascularization procedures, valvular procedures, OR any major surgical procedure within 3 months prior to the Screening Visit;
6. Acute coronary syndrome, stroke or transient ischemic attack (TIA) within 3 months prior to the Screening Visit;
7. Obstructive or restrictive cardiomyopathy, infiltrative diseases of the myocardium (e.g., amyloid, sarcoid, etc.) myocarditis, or reductions in LV function thought to be secondary primarily to valvular heart disease, prior cardiac valve surgery or known aortic stenosis;
8. The presence or anticipated placement of any pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT) devices during the ensuing 6-week study period;
9. Presence of second degree or advanced heart block;
10. Uncontrolled hypertension defined as a systolic blood pressure > 160 mmHg or a diastolic blood pressure > 110 mmHg on at least two consecutive readings;
11. Presence of any left ventricular thrombus, pericardial disease, uncorrected thyroid disease or a dyskinetic left ventricular aneurysm;
12. History of cancer that causes symptoms, disabilities, or is likely to lead to hospitalization or treatment in the next 12 months;
13. Currently receiving treatment with chemotherapeutic agents or immunosuppressant

agents or has received prior radiation therapy to the chest;
14. Liver enzymes (alanine aminotransferase [ALT] AND/OR aspartate aminotransferase[AST]) elevation > 3 times the upper limit of normal (ULN;
15. Total bilirubin > 1.5 times ULN in the absence of Gilbert*s Syndrome;
16. Bleeding diathesis or any known blood dyscrasia;
17. Anemia, defined as hemoglobin < 9 g/dL or planned blood transfusions in the next 6 weeks;
18. Estimated glomerular filtration rate (eGFR) < 30 mL/min, using the Modification of Diet in Renal Disease (MDRD) Study equation;
eGFR (mL/min/1.73 m2) = 175 x (Scr)^[-1.154] x (Age)^[-0.203] x (0.742 if female) x (1.212 if African American);
19. History of hepatitis B, hepatitis C or Human Immunodeficiency Virus (HIV) infection, or diagnosis of immunodeficiency;
20. Known active drug or alcohol abuse within 1 year of the Screening Visit. Alcohol abuse is defined as 15 or more drinks for men per week or 8 or more for women;
21. Recipient of any investigational drugs, stem cell or gene therapies, or devices OR participation in another clinical trial, within 3 months prior to the Screening Visit;
22. Any significant acute or chronic medical or psychiatric illness that, in the judgment of the Investigator, could compromise the subject*s safety, limit subject*s ability to complete the study, and/or compromise the objectives of the study;
23. Female subjects who are pregnant, planning to become pregnant, or lactating;
24. Currently requiring any changes in doses of cardiovascular medication (including diuretics) in order to control worsening of HF symptoms;
25. Known allergy to gadolinium;
26. Currently receiving treatment with therapeutic doses of anticoagulants. Antiplatelet therapy used to prevent cardiovascular disease (primary prevention) or to treat chronic disease (secondary prevention) is permitted, as well as vitamin K antagonists;
27. Currently receiving treatment with sacubitril/valsartan or trimetazidine.

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-08-2016
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bendavia
Generic name:	elamipretide

Ethics review

Approved WMO Date:	26-01-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	12-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-07-2017
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
EudraCT	EUCTR2014-005724-10-NL
CCMO	NL56002.042.16