A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Cardiac and Renal Effects of Short Term Treatment with Elamipretide in Patients Hospitalized with Congestion due to Heart Failure

Published: 25-07-2016
Last updated: 16-04-2024

Primary* To evaluate the ability of elamipretide compared to placebo to improve cardiac function measured by a reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) up to Day 8 ((or at discharge if earlier) in patients hospitalized with...

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

Summary

ID

NL-OMON45920

Source
ToetsingOnline

Brief title
Improving Diuresis and Dropsy with Elamipretide in Advanced Heart Failure

Condition

- Heart failures

Synonym
Congestion due to heart failure

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Cardiac & renal effects, Congestion, Elamipretide, Heart failure

Outcome measures

Primary outcome

Change in NT-proBNP between Baseline and Day 8/Early Discharge

Secondary outcome

* To evaluate the effect of elamipretide on changes between baseline and both

Day 3 and Day8/Earlier Discharge on:

o renal function (eGFR as per MDRD)

o body weight

o body weight per mg of furosemide administered

* Clinical status (e.g patients and physician global assessment and treatment

failures) at Day 3 and Day 8

* The average daily dose of diuretic (furosemide * adjusted for thiazide dose

if administered) between baseline and Day 3 and Day 8/Early Discharge

* The safety and tolerability of elamipretide

* The plasma pharmacokinetics (PK) of elamipretide, its metabolites, and

furosemide following a single dose and multiple doses of elamipretide in a

selected number of patients

Pharmacokinetics

The following plasma PK parameters will be determined for elamipretide

(MTP-131), its metabolites (M1 and M2), and furosemide where possible and

appropriate:

* Day 1: Cmax, Tmax, AUC(0-last), AUC(0-inf), AUC%extrap, t*, Cl, Vd, MRT

* Day 7: Cmin,ss, Cmax,ss, Tmax, AUC(0-tau),ss, AUC(0-last), AUC(0-inf),

AUC%extrap, t*, Vd

* Additional Parameters:

- Cmax, Cmin on Days 2 - 6

- P/T fluctuation (%) under steady state conditions, accumulation ratio for

Cmax and AUC(0-tau)

Study description

Background summary

Elamipretide acts upon mitochondrial cardiolipin and is believed to improve the function of the mitochondrial respiratory chain, reduce free-radical production and increase adenosine triphosphate (ATP) production. It is organ *agnostic* and thus could improve function in the kidney, liver, blood vessels, skeletal muscle and brain as well as the heart. Its multi-organ potential beneficial actions on function and metabolism observed in vitro and in animal models make it a promising candidate for targeting the complex interplay of factors that ultimately result in the syndrome of clinical heart failure. In a small study of patients with chronic heart failure, a single four-hour infusion of elamipretide acutely reduced both end-diastolic and end-systolic volumes determined by echocardiography. In an animal model of renal insufficiency, elamipretide improved renal blood flow, glomerular filtration rate and attenuated the extent of tubular injury and fibrosis. It represents an important opportunity to address a critical and unmet clinical need.

Study objective

Primary
* To evaluate the ability of elamipretide compared to placebo to improve cardiac function measured by a reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) up to Day 8 ((or at discharge if earlier) in patients hospitalized with congestion due to heart failure

Secondary
* To evaluate the effect of elamipretide on changes between baseline and both Day 3 and Day 8/Early Discharge on:
o renal function (eGFR as per MDRD)
o body weight
o body weight per mg of furosemide administered
* Clinical status (e.g. patients and physician global assessment and treatment failures) at Day 3 and Day 8
* The average daily dose of diuretic (furosemide * adjusted for thiazide dose if administered) between baseline and Day 3 and Day 8/Early Discharge
* The safety and tolerability of elamipretide
* The plasma pharmacokinetics (PK) of elamipretide, its metabolites, and furosemide following a single dose and multiple doses of elamipretide in a selected number of patients

Study design

A prospective, randomized, double-blind, parallel-group, placebo-controlled, multiple dose study comparing placebo and elamipretide given intravenously daily for up to 7 days to patients requiring an intravenous infusion of furosemide for the treatment of congestion complicating heart failure.
Patients will be consented, have baseline investigations, be initiated (or continued) on an intravenous infusion of furosemide at 10mg/hour and subsequently randomized to either elamipretide or placebo within 72 hours (ideally between 12 and 36 hours) of hospital presentation. Patients will continue the intravenous infusion of furosemide ideally for at least 48 hours, however the dose can be modified if dictated by the clinical situation.
Patients who clinically improve sufficiently for discharge prior to Day 8, in the opinion of the Investigator, may receive less than 7 days of treatment. Please note that patients being discharged earlier than Day 8 should receive the last dose of treatment on the day of discharge.
Safety will be assessed starting at randomization up to Day 40. There will be two Safety Visits after discharge, one at Day 21 and one at Day 40.
Efficacy will be evaluated by assessing changes in NT-proBNP, body weight, body weight/mg furosemide, total dose of diuretics, eGFR, and patient reported outcomes. Safety will be evaluated by assessing adverse events and serious adverse events, vital signs, ECGs, and laboratory evaluations. At selected sites, samples for plasma PK analysis of elamipretide, its metabolites, and furosemide will be collected. An independent Data and Safety Monitoring Board (DSMB) will assess subject safety during the trial.

Intervention

All patients will receive the following interventions:
- ECG
- Blood draws for safety (chemistry and hematology)
- Blood draws for pharmacokinetic parameters at selected sites
- Echocardiography at selected sites
- Daily IV infusion of IP or placebo for 7 days
- IV infusion of furosemide for 48 hours followed by tablets upon investigator decision

Study burden and risks

4.2.1. Potential Benefits
In animal models of heart failure, elamipretide has shown promising effects on several potential therapeutic targets for heart failure. In canine studies of severe, well-established heart failure both a single infusion and 3 months of daily elamipretide injections improved left ventricular
(LV) ejection fraction, LV end diastolic pressure, and rate of rise of LV pressure (dP/dtmax), without changes in heart rate or mean aortic pressure. In murine models of heart failure, elamipretide ameliorated cardiac hypertrophy and enlargement, systolic and diastolic dysfunction, and myocardial fibrosis. The effects of elamipretide on cardiac function assessed by echocardiography were assessed in a Phase 1 trial (SPIHF-101) evaluating single ascending intravenous (IV) doses in 24 patients with moderate chronic heart failure receiving concomitant standard of care pharmacological therapy for chronic heart failure. An independent blinded core lab analysis by Duke Clinical Research Institute suggested that the highest dose of elamipretide (0.25 mg/kg/hr administered intravenously over 4 hours) improved mean LV end systolic volume (absolute change from baseline -11.1 mL versus 1.5 mL for placebo; mean difference = -12.6 mL; p=.0157) and mean LV end diastolic volume (absolute change from baseline -17.9 mL versus 2.9 mL for placebo; mean difference = -20.8 mL; p=.002) at the end of the infusion. These changes occurred in the absence of any heart rate or blood pressure change. These findings, after a single dose of elamipretide, suggest beneficial effects that require further investigation with repeat dosing.
There are currently two additional ongoing studies with elamipretide in subjects with heart failure. These trials are investigating the effects of 28 days of subcutaneous (SC) therapy of elamipretide. The SPIHF-201 study is investigating the effects of 4 mg and 40 mg of elamipretide on left ventricular function in approximately 45 subjects with stable heart failure with reduced ejection fraction (HFrEF). The SPIHF-203 study is investigating the effects of 40 mg of elamipretide on left ventricular function in approximately 45 subjects with stable heart failure with preserved ejection fraction (HFpEF).

4.2.2. Potential Risks

4.2.2.1. Safety findings * Nonclinical studies

Toxicology studies in rats and dogs showed that elamipretide has an acceptable profile that permits clinical investigations in humans for the proposed duration of the study.

In rats and dogs, no safety issues relevant to either IV infusion or SC administration at therapeutic doses were identified during the non-clinical evaluation of elamipretide. Elamipretide did not cause end-organ toxicity at any dose tested in either rats or dogs. Systemic toxicity at high doses was manifested primarily by acute and transient clinical signs, which may have been mediated by histaminergic-like reactions. Effects were associated with maximum elamipretide plasma concentration (Cmax) and were rapidly reversible as plasma concentrations of elamipretide and histamine decreased. Dose administration was not associated with any adverse effects on cardiovascular, respiratory or central nervous system function; off-target non-adverse effects were limited to transient decrease of blood pressure and increase in heart rate, which is thought to be consistent with histaminergic-like reactions. In all studies, the severity of the effects was proportional to Cmax for elamipretide; thus, the safety margin is estimated based on Cmax, and not area under the plasma-concentration-time curve (AUC). The plasma elamipretide threshold concentration for clinically-relevant adverse effects appears to be ~20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum anticipated human exposures. Local injection site reactions evident upon SC administration varied with species, dose and dose concentration. In rats, it was determined that 40 mg/day and 40 mg/mL, respectively, were well tolerated. Elamipretide did not show genotoxicity in the full battery of tests and caused no significant haemolysis or inhibition of receptor binding. Elamipretide was not associated with adverse effects on fertility or embryo-fetal development. No formal immunotoxicity studies have been performed. As a tetrapeptide the immunogenic potential of the drug is expected to be low.

4.2.2.2. Human safety

The safety profile of 7 daily IV doses of elamipretide has not yet been evaluated in heart failure patients.

In 7 completed single-dose IV trials in healthy subjects, the most commonly reported treatment emergent adverse events (TEAEs) in subjects dosed with elamipretide were headache, nausea, and hyponatremia. Across the 3 trials evaluating single IV doses of elamipretide in cardio-renal patient populations (i.e., chronic heart failure, acute kidney injury, and acute coronary syndrome), single IV doses of elamipretide were generally safe and well tolerated with no notable differences between the elamipretide and placebo treatment groups in the frequency or severity of adverse events.

Both single-dose SC administration and multiple-dose SC administration for seven days were well tolerated in healthy adult subjects at doses up to 40 mg. No deaths or drug-related serious adverse events (SAEs) occurred, and no subjects withdrew from the study for drug-related reasons. The most commonly reported TEAE in the elamipretide treatment group was mild injection site pruritus, reported with similar frequency after single and multiple doses.

Patients with chronic heart failure: Single elamipretide doses up to 1 mg/kg administered IV over 4 hours were safe and well-tolerated in 24 patients with stable chronic heart failure in a Phase 1 trial. No SAEs or deaths were recorded. A total of four TEAEs were reported in three elamipretide-treated subjects: worsening renal failure, dyspnea, tachycardia, and low haemoglobin. These events were assessed by the investigator to be of mild or moderate severity and unrelated to study drug.
Patients with first-time anterior ST-segment elevated myocardial infarction (STEMI) undergoing primary PCI for a proximal or mid left anterior descending (LAD) artery occlusion: 297 subjects received elamipretide or placebo (1:1 randomization) infused at a rate of 0.05 mg/kg/h for 1
hour. Study drug was administered for *15 minutes, but < 60 minutes prior to PCI and for 1 hour following reperfusion. Elamipretide was safe and well tolerated. There were no significant differences in arrhythmias, deaths, SAEs, TEAEs or in the incidence of hyponatremia between
the elamipretide patients and the controls. There were 3 deaths (1 stroke on day 18, 1 shock due to coronary artery dissection during angioplasty and 1 sudden death on day 7) in the elamipretide-treated patients and 1 death (multi-organ failure on day 13) in the placebo-treated patients within the first 30 days after STEMI.
There have been no pregnancies, exposures during lactation, overdoses, abuses or misuses, or medication errors reported thus far in the elamipretide clinical program.

4.2.3. Conclusions
In summary, based on the clinical and non-clinical study data, acceptable safety risks are expected for the proposed current study. Hence the benefit:risk ratio of this study is considered favourable.

Contacts

Public
Stealth BioTherapeutics Inc.

Grove Street 275
Newton MA02466
US
Scientific
Stealth BioTherapeutics Inc.

Grove Street 275
Newton MA02466
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. Aged *18 years
3. A history of chronic heart failure for at least 1 month
4. Treated with *40 mg/day of furosemide or bumetanide *1 mg/day or torasemide *10 mg/day for at least 1 month
5. In-hospital observation/admission and treatment for *72 hours and primary cause for admission is heart failure with persistent congestion in the opinion of the Investigator (i.e. at least +2 pitting oedema and/or an estimated 8 kg gain in weight over baseline over the past 4 weeks) requiring intravenous loop diuretic therapy
6. Able to be weighed
7. Sufficiently severe oedema to justify treatment by an intravenous infusion of furosemide of 10 mg/hour for at least 48 hours
Note: dose should be modified if dictated by the clinical situation and should be adjusted to the patient*s needs
8. Systolic blood pressure >/<=90 mmHg and considered to be haemodynamically stable, in the opinion of the Investigator
9. History of left ventricular ejection fraction (LVEF) *40% confirmed in the last 18 months
10. NT-proBNP >1500 pg/ml or BNP >500 pg/ml
11. An eGFR of >/<=30 mL/min/1.73 m2 using the 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)
12. 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 drug:
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 a 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)
13. Willing to adhere to the study requirements for the length of the trial

Exclusion criteria

1. Completely bedridden for >2 weeks prior to admission. Patients should at least have been able to go the toilet and back and to get out of bed for meals at some time during this period
2. Known intolerance of furosemide
3. Acute coronary syndrome, stroke, or transient ischemic attack (TIA), coronary or peripheral revascularization procedures, valve procedures, OR any major surgical procedure within the previous 6 weeks
4. Invasive cardiac investigation and/or treatment (i.e. coronary angiography, percutaneous coronary intervention [PCI] or surgery) or other surgical procedure planned in the next 4 weeks
5. Use of intravenous radiographic contrast agent within 72 hours prior to screening or planned use during the study
6. Severe, in the investigators opinion, uncorrected valve disease or congenital heart disease as the cause for cardiac decompensation
7. Acute mechanical cause of decompensated heart failure such as papillary muscle rupture
8. Obstructive or infiltrative cardiomyopathy (e.g. amyloid, sarcoid, etc), suspected acute myocarditis, or heart failure related to an untreated metabolic condition (e.g. haemochromatosis)
9. Second or third degree heart block unless the subject has a ventricular pacemaker
10. Atrial fibrillation/flutter with sustained ventricular response of >130 bpm
11. Placement of a ventricular resynchronization device within the previous 6 weeks
12. Treatment or planned treatment with intravenous inotropic agents other than digoxin at any time on this admission
13. Receipt of intravenous vasodilator therapy * 6 hours prior to randomization
14. The presence of any mechanical assist device or listed for or a history of a heart transplant
15. Suspected systemic infection or pneumonia and/or the need for antibiotic treatment between admission and time of consent. Patients given antibiotics without clear justification can be included as long as it is appropriate to discontinue the antibiotics
16. Severe respiratory disease or anticipated need for mechanical respiratory support (i.e. mechanical ventilation)
17. Anuric in the previous 24 hours
18. Haemoglobin <9 g/dL at screening or planned blood transfusions in the next 30 days
19. Serum potassium >5.5 mEq/L
20. Marked proteinuria suggestive of nephrotic syndrome

21. Estimated GFR (eGFR) as per MDRD equation <30 ml/min
22. Serum albumin of < 2.8 g/dL
23. Liver enzymes (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) elevation >5 times the upper limit of normal (ULN)
24. Total bilirubin >2.0 times ULN in the absence of Gilbert*s Syndrome
25. Known active hepatitis B, hepatitis C or Human Immunodeficiency Virus (HIV) infection, or diagnosis of immunodeficiency
26. Known active drug or alcohol abuse within 1 year of the Screening Visit at the discretion of the Investigator (i.e. 15 or more drinks for men per week or 8 or more for women).
27. Currently receiving treatment with chemotherapeutic agents or immunosuppressant agents or having received prior radiation therapy to the chest
28. Current or planned ultrafiltration, paracentesis, haemofiltration or dialysis
29. Currently receiving treatment with any intravenous steroid or > 5 mg of oral prednisone (or equivalent)
30. Recipient of stem cell or gene therapy or current therapeutic investigational devices
31. Participation in another clinical trial with an investigative product within 3 months prior to the Screening Visit
32. Any significant acute or chronic medical or psychiatric illness or social situation that, in the judgment of the Investigator, could compromise a subject*s safety, limit subject*s ability to complete the study and follow-up period, and/or compromise the objectives of the study
33. Women who are pregnant, planning to become pregnant, or lactating
34. Currently receiving treatment with therapeutic doses of any of the novel or direct oral anticoagulants (vitamin K antagonist are permitted)
35. Currently receiving treatment with sacubitril (Entresto*)
Note: This is because, currently, there is a lack of interaction data available
36. Hypersensitivity to elamipretide or any of its excipients

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):	05-01-2017
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	25-07-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-10-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-11-2017
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	EUCTR2016-000126-19-NL
CCMO	NL57646.042.16