# A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Dutogliptin in Combination with Filgrastim in Early Recovery Post-Myocardial Infarction

Published: 25-05-2018
Last updated: 12-04-2024

Primary ObjectiveTo evaluate the safety and tolerability of dutogliptin in combination with filgrastim in subjects with STEMI compared with placebo Secondary ObjectivesTo assess preliminary efficacy of dutogliptin in combination with filgrastim in...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Myocardial disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48797

**Source**
ToetsingOnline

**Brief title**
REC-DUT-002

### Condition

- Myocardial disorders

**Synonym**
'heart attack', 'myocardial infarction'

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** RECARDIO Inc.
**Source(s) of monetary or material Support:** RECARDIO Inc. (sponsor)

## Intervention

**Keyword:** Combination therapy, Myocardial Infarction, Regenerrative, Stem cell

## Outcome measures

### Primary outcome

Safety Endpoints:

Safety assessments will include reporting of AEs and serious AEs (SAEs),

clinical laboratory tests, ECGs, vital signs, and physical examinations.

Primary Efficacy Endpoints:

Change from baseline to Day 90 (Month 3) in the following cardiac functional

parameters as assessed by central, blinded review of cMRI:

- Left ventricular ejection fraction (LVEF)

- Left ventricular end systolic volume (LVESV; absolute and indexed)

- Left ventricular end diastolic volume (LVEDV; absolute and indexed)

- Infarct size

- Left ventricular mass (absolute and indexed)

- Regional wall motion

### Secondary outcome

Secondary Efficacy Endpoints:

- Individual clinical endpoints, including recurrent non-fatal MI, non-fatal

stroke, death due to any cause, cardiovascular (CV) death (death due to acute

MI, chronic heart failure [CHF], stroke, or sudden cardiac death), stent thrombosis or CHF hospitalization.

- Combined clinical endpoints, including major adverse cardiac events, defined as non-fatal MI, non-fatal stroke, CV death, stent thrombosis, and CHF hospitalization

- Time to cardiovascular event, as defined by the time from Randomization to the first occurrence of recurrent non-fatal MI, non-fatal stroke, death due to any cause, stent thrombosis, and CHF hospitalization

Exploratory Endpoints:

Change from baseline in plasma biomarkers NT-proBNP and high sensitivity troponin.

PK/PD Endpoints (in selected centers):

- Plasma dutogliptin concentration profiles (PK)

- Trough dutogliptin concentrations

- Maximum plasma concentration (Cmax)

- Time corresponding to Cmax

- Area under the drug concentration-time curve

- Additional parameters may also be determined (volume of distribution, clearance and terminal phase half-life)

Plasma DPP4 activity (PD)

- Maximum effect on plasma DPP4 activity (Emax)

- Trough plasma DPP4 activity

Change from baseline in plasma SDF-1* levels.

# Study description

**Background summary**

Pre-clinical studies have demonstrated that G-CSF-based stem cell mobilization in combination with genetic or pharmaceutical CD26/DPP4 inhibition after acute MI results in improved cardiac homing of stem cells, enhanced heart function, and increased survival. In mice, combining genetic and pharmacologic inhibition of DPP4 with G-CSFmediated stem cell mobilization after MI led to (1) decreased myocardial DPP4 activity,
(2) increased myocardial homing of circulating CXCR-4+ stem cells, (3) reduced cardiac remodeling, and (4) improved heart function and survival [Zaruba, 2009; Theiss, 2013; Nix2016].

In a Phase 1 study in healthy volunteers, dutogliptin was administered as single and multiple daily SC doses ranging from 30 to 120 mg. Inhibition of plasma DPP4 increased in duration with increasing dose. However, complete (*80%) inhibition could not be achieved for 24 hour with daily doses up to 120 mg. Sustained inhibition was observed to last for 8*12 hours following a single 60 mg dose, therefore twice daily 60 mg dosing has been selected as the active dose for this study. Once daily doses up to 120 mg were well tolerated in the Phase 1 study.

The current study will investigate the safety and efficacy of dutogliptin administered in combination with filgrastim compared with placebo in subjects with ST-elevation myocardial infarction (STEMI) who are successfully revascularized following percutaneous coronary intervention (PCI) and stent implantation.

**Study objective**

Primary Objective
To evaluate the safety and tolerability of dutogliptin in combination with filgrastim in subjects with STEMI compared with placebo

Secondary Objectives
To assess preliminary efficacy of dutogliptin in combination with filgrastim in subjects with STEMI compared with placebo

To determine the pharmacokinetics (PK) of dutogliptin in a subset of the study population
To establish the pharmacodynamics (PD) of dutogliptin (plasma dipeptidylpeptidase-IV (DPP4) activity) in a subset of the study population

Exploratory Objectives
To examine the effects of dutogliptin in combination with filgrastim on:
Change from baseline in plasma stromal cell-derived factor (SDF)-1a levels
Change from baseline in plasma biomarkers N-terminal pro-b-type natriuretic peptide (NTproBNP) and high sensitivity troponin

Note: This is an international study, which is conducted in the US as well as Europe. In addition to the objectives that are assessed in Europe as well as US, PK/PD data are collected in the US only. However, even if PK/PD data are not assessed in EU, this assessment is part of the study design and hence described in the protocol. As the study needs to be considered in its entirety, the information on assessments performed in the US only cannot be excluded when describing the study for other involved countries.

**Study design**

Study REC-DUT-002 is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and preliminary efficacy of dutogliptin administered in combination with filgrastim in subjects with STEMI following PCI and stent implantation. 140 evaluable subjects will be randomized in this study in order to have 110 subjects complete the study.

**Intervention**

Dutogliptin 60 mg administered by twice daily subcutaneous (SC) injection for 14 days in combination with a fixed standard dose of filgrastim (10 *g/kg) administered SC daily for 5 days

**Study burden and risks**

Subjects will be screened for eligibility as soon as possible after hospital admission for treatment of STEMI. Eligible subjects will have received local standard of care procedures including PCI and stent implantation (bare metal or drug-eluting). The allowable time between onset of STEMI symptoms and stent implantation is >2 and <24 hours.
Eligibility for study randomization will be evaluated in a step-wise manner. It is recommended that medical history, physical examination, and safety laboratory screening tests are completed prior to conducting the cardiac echocardiography (cECHO). Subjects who do not meet all eligibility criteria will be considered ineligible and will not be randomized.
Eligible subjects will be randomized in a 1:1 ratio to receive twice daily SC

injections of 60 mg dutogliptin for 14 days in combination with 10 *g/kg filgrastim for 5 days or matching dutogliptin placebo for 14 days in combination with matching filgrastim placebo for 5 days. Subjects must be randomized and study treatment initiated within 36 hours after stent implantation. Study treatment will be administered SC to subjects by the site hospital staff at the Day 1 visit and while the subject remains hospitalized. Upon discharge, adequate supplies of investigational medicinal products (IMPs) to complete all dosing will be issued to the homes care nursing service who will administer all remaining doses to the subject at home. The homecare nursing service will be blinded to study allocation.

Safety assessments will be performed on Day 1 (baseline), Day 3 or day of discharge if before Day 3, Day 15 and Day 90 (Month 3). Safety assessments will include physical examinations, vital signs, and an assessment of adverse events (AEs) at each time point.

An independent Data Safety Monitoring Board (DSMB) will review study data following completion of Day 90 by the initial 30 subjects and evaluate if it is appropriate to continue the study according to the protocol. The DSMB may recommend changes in the conduct of the study to the Sponsor to ensure subject safety. The DSMB will meet and review the study data at least biannually and make safety recommendations to the Sponsor.
Efficacy assessments will be performed within 72 hours after PCI (baseline) and on Day 90. Efficacy assessments will include an evaluation of cardiac functional parameters as determined by cardiac magnetic resonance imaging (cMRI) and individual and combined clinical endpoints.

Electrocardiograms (ECG), clinical laboratory tests, and exploratory assessments will be performed at selected time points. Exploratory assessments will include changes in biomarker concentrations and in selected centers an evaluation of plasma dutogliptin concentrations (PK) and pharmacodynamics (PD) changes (DPP4 and SDF-1*).

The patient only will come back to study site for D15 and D90 visit.

There is no guarantee that the patient will benefit from this study and taking part in this study may or may not cause his health to improve. Information from this study may help doctors learn more about Dutogliptin and the regenerative treatment of his condition.

What are the risks?
There are possible risks, disadvantages and inconveniences with any research study:
risks of tests and procedures (more tests and procedures, study visits could take more time), blood tests (pain where the needle is inserted, and there is a small risk of bruising or infection at this location, dizziness, upset stomach, or fainting), injection site reactions (some rash, pain/tenderness, blistering

or ulcers), ECG risks (skin irritation from the ECG electrode pads, pain when the pads are removed), MRI Scan (claustrophobie, noisy), side effects of Filgrastim (mild to moderate bone pain, allergic reactions, affect pregnancy), side effects of Dutogliptin (headache, stomach discomfort, diarrhoea, passing wind and frequent bowel movements nausea, dizziness)

This is the first study in which the drug will be delivered by an injection and to patients following a heart attack and the placement of a stent. There may be some additional risks of use that are unknown right now. Furthermore the safety of Dutogliptin during pregnancy and breast feeding are not known as well as the effects of Dutogliptin and Filgrastim on sperm.

## Contacts

**Public**
RECARDIO Inc.

1 Market Street Spear Tower, 36th
San Francisco CA 94105
US
**Scientific**
RECARDIO Inc.

1 Market Street Spear Tower, 36th
San Francisco CA 94105
US

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

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

## Inclusion criteria

1. Male or female,age 18 to 85 (having reached 18 and before having reached 86 at the time of ICF signing).
2. Body weight <96 kg (~212 lb).
3. Able to provide written informed consent, including signing and dating the ICF.
4. Diagnosis of STEMI (defined as new ST-segment elevation at the J point of at least 2 continuous leads of >2 mm [0.2 mV] in men or >1.5 mm [0.1 mV] in women in leads V2 and V3 OR >1 mm in any other contiguous precordial leads or the limb leads [for both men and women]) with PCI (bare metal or drug-eluting stent) and Thrombolysis in Myocardial Infarction flow grade 2 or 3 occurring up to 24 hours after symptom onset (to time of first balloon inflation).
5. Left ventricular ejection fraction (LVEF) *45% obtained by cECHO performed within 36 hours post-stent placement.
6. Receiving standard medical therapy for post-myocardial infarction (MI) treatment, according to local procedures and Principal Investigator's discretion.
7. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and an additional negative urine pregnancy test prior to the first dose of IMP unless regulated differently by national legislation.
8. Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during treatment and for 4 weeks after the last dose.

## Exclusion criteria

1. Previous MI prior to Screening.
2. Complex peri/post-MI clinical course, including arrhythmias, cardiogenic shock, pulmonary edema requiring mechanical ventilation, or requirement for vasopressor medications.
3. Significant pre-existing cardiomyopathy with known LVEF *45% or moderate to severe mitral or aortic valvular disease.
4. Amyloidosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis.
5. Existing heart transplant.
6. Ventricular tachycardia or fibrillation not associated with an acute ischemic episode.
7. Uncontrolled hypertension (systolic >180 mmHg or diastolic >120 mmHg).

8. Treatment with any DPP4 inhibitors (e.g., alogliptin, linagliptin, vildagliptin, saxagliptin, sitagliptin) or granulocyte-colony stimulating factor medication (e.g., filgrastim, lenograstim, pegfilgrastim, lipegfilgrastim) within 4 months prior to Randomization.
9. Contraindication to treatment with filgrastim, including known allergy to filgrastim or other G-CSF medication.
10. Anemia defined as hemoglobin <9 g/dL prior to Randomization.
11. Thrombocytosis (platelets > 500 k/uL).
12. Known positive serology for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV), any other indication of liver disease or injury.
13. ALT concentrations >3 times the upper limit of normal (ULN) and bilirubin (TBL) >2 x ULN, or INR >1.5 prior to Randomization, according to local laboratory assessments, and/or any indication of liver disease or injury. If ALT is between >3 and 8 x ULN, and all other admission criteria are met, the test may be repeated within the time window before Randomization.
14. History of cirrhosis and Child-Pugh score B or C.
15. Current fever greater than 101.4 °F (38.6 °C) or recent systemic infection within 2 weeks prior to Randomization.
16. Contraindication to cMRI procedure, including prior implantable cardioverter defibrillator placement, known reaction to gadolinium, claustrophobia, non-MRI-compatible, cochlear implant, obesity, or presence of ferromagnetic material including shunts, shrapnel, penile prostheses, or blood vessel coil.
17. Pregnant, planning to become pregnant, or nursing female subjects.
18. Autoimmune disease requiring immunosuppressive therapy or chronic steroid treatment >5 mg/day prednisolone or equivalent.
19. Significant renal impairment defined as estimated glomerular filtration rate <45 mL/min/1.73 m2, using the Chronic Kidney Disease Epidemiology Collaboration equation.
20. Active neoplasm requiring surgery, chemotherapy, or radiation within the prior 12 months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence are allowed).
21. Malignant hematological disease, i.e., chronic myeloid leukemia or myelodysplastic syndrome.
22. History of cerebrovascular accident or transient ischemic attack in the past 6 months.
23. History of pneumonia in the last 4 weeks.
24. History of any significant medical or psychiatric disorder that in the opinion of the investigator would make the subject unsuitable for participation in the study.
25. Treatment with an investigational drug within 30 days or five halflives(whichever is longer) or treatment with an investigational biologic drug within 6 weeks prior to randomization.
26. Participation in another concurrent clinical trial involving a therapeutic intervention (participation in observational studies and/or registry studies is permitted).

27. Unable or unwilling to comply with the requirements of the study.
28. Subject and/or an immediate family member is an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization.
29. Considered by the investigator to be unsuitable to participate in the study for any other reason.
30. Persons who are in an institution as a result of an administrative or judicial order, or soldiers.
31. History of alcohol or drug abuse.

# 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): | 17-02-2020 |
| Enrollment: | 10 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Dutogliptin |
| Generic name: | Dutogliptin tartrate |
| Product type: | Medicine |
| Brand name: | Neupogen |
| Generic name: | Filgrastim |

| | |
|---|---|
| Registration: | Yes - NL outside intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 25-05-2018 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 29-11-2018 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 24-12-2019 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 29-01-2020 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

## 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 | EUCTR2018-000916-75-NL |
| ClinicalTrials.gov | NCT03486080 |
| CCMO | NL65070.068.18 |