

Assessment of efficacy of mirabegron, a new beta3-adrenergic receptor in the prevention of heart failure

Submission date 28/10/2015	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 30/10/2015	Overall study status Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 11/10/2023	Condition category Circulatory System	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Background and study aims

Heart failure (HF) is a medical condition caused by the heart not being able to pump enough blood around the body at the right pressure. Symptoms include breathlessness, feeling very tired and ankle swelling. Patients can be split into one of two groups, depending on the type of heart failure that they have. HF caused by the part of the heart that pumps blood around the body (left ventricle) becoming weak is called heart failure with left ventricular systolic dysfunction or heart failure with reduced ejection fraction (HFREF). Heart failure caused by the left ventricle becoming stiff, making it more difficult for the heart chamber to fill with blood is called heart failure with preserved ejection fraction (HFPEF). As HF is a progressive disorder increasing with age, the proportion of these patients is rising due to the aging of the population. Beside costs, HFPEF also puts a heavy burden on the quality of life of (mostly elderly) patients, with a loss of independence and repeated hospitalisations. Therefore, HFPEF is a chronic, costly, debilitating disease. A major contributor to HFPEF is myocardial (heart) remodelling, e.g. hypertrophy (abnormal growth of heart muscle) and fibrosis, as well as cellular functional /structural modifications leading to changes in how the heart contracts (contractile properties) and ventricular distensibility (distending of the left ventricle). Unfortunately, there are currently no evidence-based treatment strategies for this. This study will look at a novel therapeutic concept: β 3AR activation to reduce/prevent cardiac remodeling. Recently, a new drug, called mirabegron has been developed and marketed for clinical use in overactive bladder disease. This study will test if the drug can also be used for the prevention of cardiac remodeling leading to HFPEF. Previous studies have shown that activation of β 3AR reduces myocardial hypertrophy and fibrosis without affecting the function of the left ventricle. Therefore, the recent availability of this new drug offers the possibility to test the potential benefit of mirabegron as a therapy in addition to standard care (add-on therapy) to prevent/delay myocardial remodelling in patients at high risk of developing HFPEF.

Who can participate?

Patients with structural cardiac disease with or without HF symptoms.

What does the study involve?

Participants are randomly allocated to one of two groups. Those in group 1 are given mirabegron. Those in group 2 are given a placebo. They are then all monitored for change in left ventricular mass (i.e. change in the size of the left ventricle) (assessed by MRI) and/or changes in diastolic function (loss of ventricle function) (assessed by echocardiography) over the next 12 months.

What are the possible benefits and risks of participating?

Benefits of taking part for participants include close monitoring and treatment of high blood pressure, according to most recent guidelines, as well as protection from the development of heart failure with preserved ejection fraction, a frequent form of heart failure in the targeted patient population. Possible risks are side effects of the test drug, mirabegron but previous studies have suggested that this risk is small.

Where is the study run from?

A total of 11 medical centres and university hospitals in Belgium, France, Germany, Greece, Portugal, Italy, Poland and the UK.

When is the study starting and how long is it expected to run for?

March 2016 to September 2022

Who is funding the study?

European Commission (Horizon 202 grant)

Who is the main contact?

1. Professor Jean-Luc Balligand (scientific)
2. Dr Christophe L. Depoix (public), christophe.depoix@uclouvain.be

Contact information

Type(s)

Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)

2015-003146-75

ClinicalTrials.gov (NCT)

NCT02599480

Protocol serial number

Beta3_LVH V1.0

Study information

Scientific Title

A multi-centre randomized, placebo-controlled trial of mirabegron, a new beta3-adrenergic receptor agonist on the progression of left ventricular mass and diastolic function in patients with structural heart disease

Acronym

Beta3_LVH

Study objectives

The primary objective is to evaluate the effect of mirabegron (a new β 3-specific agonist) on top of standard treatment on change in left ventricular mass and/or changes in diastolic function after 12 months of treatment in patients with cardiac structural remodeling with or without symptoms of heart failure (maximum NYHA II).

Ethics approval required

Ethics approval required

Ethics approval(s)

approved 16/03/2016, Le Comité d'Ethique Hospitalo-Facultaire Saint-Luc - UCL (Promenade de l'Alma 51 bte B1.43.03, Brussels, 1200, Belgium; +32 2 764 55 14; comission.ethique-saintluc@uclouvain.be), ref: 2015/01DEC/655

Study design

Interventional prospective multi-centre randomized placebo-controlled trial

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Structural heart disease (hypertrophic cardiac remodeling, stage B AHA) at high risk for developing HFpEF (heart failure with preserved ejection fraction).

Interventions

This is a two armed, prospective, randomized, placebo-controlled, multi-centric international phase IIb trial with placebo and mirabegron distributed in a 1:1 fashion. The patients enrolled will have cardiac structural remodeling with or without symptoms of heart failure (maximum NYHA II).

Patients will be monitored for change in left ventricular mass (assessed by RMI) and/or changes in diastolic function (assessed by echocardiography) after 12 months of treatment.

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

Mirabegron

Primary outcome(s)

The primary objective is to evaluate the effect of mirabegron (a new β_3 -specific agonist) on change in left ventricular mass and/or changes in diastolic function after 12 months of treatment in patients with cardiac structural remodeling with or without symptoms of heart failure (maximum NYHA II).

Two equally ranked, primary endpoints:

1. Change in left ventricular mass index (LVMI in g/m², defined as left ventricular mass divided by body surface) measured at baseline and 12 months after randomisation
2. Change in diastolic function, assessed as the ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity (E/e') measured at baseline and 12 months after randomisation

Key secondary outcome(s)

Effect of mirabegron on other parameters of diastolic heart disease, i.e. cardiac fibrosis, left atrial volume index, diastolic function (E/e'), maximal exercise capacity and laboratory markers (analysed after 6 and 12 months of mirabegron treatment).

1. Further MRI endpoints (all measured in the central MRI core lab):

- 1.1. Cardiac fibrosis at baseline and at 12 months. Fibrosis is a key pathogenic mechanism of diastolic dysfunction, which is at the origin of HFpEF
- 1.2. Left atrial volume index at baseline and at 12 months. This parameter determines diastolic filling (and was shown to predict treatment efficacy in HFpEF in the J-DHF trial (Yamamoto et al. 2013))
- 1.3. LV mass index (by cardiac MRI) at 6 months
- 1.4. Diastolic function (E/e') at 6 months

- 2. Laboratory parameters at baseline and at 3, 6 and 12 months:
 - 2.1. Serum biomarkers (Galectin3, GDF15, NT-proBNP, hsTnT)
 - 2.2. Metabolic parameters (fasting glucose, modified HOMA test, HbA1c, serum lipids)
- 3. Maximal exercise capacity (peak VO₂) at baseline, 6 and 12 months
- 4. Safety endpoints:
 - 4.1. Incidence, severity and frequency of adverse and serious adverse events
 - 4.2. Mortality

Completion date

01/09/2022

Eligibility

Key inclusion criteria

- 1. Age between 18 and 90 years
- 2. Arterial hypertension on stable therapy according to current guideline algorithms (including stable medication for at least four weeks before inclusion)
- 3. Morphological signs of structural cardiac remodelling by echocardiography, i.e. increased LV mass index (110 g/m² or higher for female; 134 g/m² or higher for male subjects (Devereux, Reichek 1977)) or end-diastolic wall thickness >13 mm in at least one wall segment
- 4. Patients may have atrial fibrillation (AF), but with well-regulated ventricular response, i.e. heart rate <100/min at inclusion (RACE II - (Groenveld et al. 2013, 2013))
- 5. Written informed consent
- 6. For subjects unable to read and/or write, oral informed consent observed by an independent witness is acceptable if the subject has fully understood oral information given by the Investigator. The witness should sign the consent form on behalf of the subject

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

Total final enrolment

296

Key exclusion criteria

- 1. Unstable hypertension with systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg (confirmed at three consecutive office measurements in sitting position); if so, the patient may be re-screened after optimization of anti-hypertensive treatment, which should be stabilized for at least four weeks before inclusion.

2. Documented ischemic cardiac disease:
 - 2.1. current angina pectoris or
 - 2.2. ischemia on stress test or
 - 2.3. untreated coronary stenosis >50% or
 - 2.4. history of acute myocardial infarction (AMI) or
 - 2.5. coronary artery bypass graft (CABG, < than 3 months prior to screening) or
 - 2.6. percutaneous transluminal coronary angioplasty (PTCA) less than 3 months prior to screening.
3. History of hospitalization for overt heart failure within last 12 months
4. Patients after heart transplantation
5. Genetic hypertrophic or dilated cardiomyopathy
6. Dysthyroidism.
7. Severe valvulopathy (less than 1 cm² aortic valve area or major mitral valve insufficiency at Doppler echocardiography)
8. NYHA-class > II
9. BMI > 40 kg/m²
10. EF < 50%, regardless of symptoms
11. Known other cause (i.e. COPD) of respiratory dysfunction; patients under positive pressure (CPAP) treatment for sleep apnea syndrome may be included, provided they have been under regular treatment for at least one year before inclusion in the study
12. eGFR < 30 ml/min
13. Abnormal liver function tests (AST or ALT >2 X upper normal limit or GGT>3x upper normal limit)
14. Type I diabetes, complicated type II diabetes (i.e. with documented coronary macroangiopathy , cfr exclusion criterion 1 or documented other vascular complication)
15. Patients with anemia (male: Hb <130 g/l, female: Hb <120 g/l)
16. Patients with bladder outlet obstruction
17. Patients using antimuscarinic cholinergic drugs for treatment of OAB
18. Current use of digitalis, bupranolol, propranolol, nebivolol (known to interfere with β 3AR signalling)*
19. Patients continuously treated with Sildenafil or other PDE5 inhibitors
20. Current use of antifungal azole derivatives (fluconazole, itraconazole, miconazole, posaconazole, voriconazole) (known inhibitors of CYP3A4, the main metabolizer of mirabegron)
21. Current treatment with mirabegron or indication for future treatment with mirabegron due to other indications
22. Contraindication for MRI (e.g. pacemaker, defibrillator, ferromagnetic devices or severe claustrophobia)
23. Pregnant or nursing women
24. Participation in any other interventional trial
25. Fertile women (within two years of their last menstruation) without appropriate contraceptive measures (hormonal implant, injections, oral contraceptives, intrauterine devices, partner with vasectomy) while participating in the trial (participants using a hormone-based method have to be informed of possible effects from the trial medication on contraception)
26. Contraindication to mirabegron (e.g. hypersensitivity) or any other components of the trial medication

* Note: patients are allowed to take a β (1-2)-blocker, other than the drugs listed above

Date of first enrolment

01/03/2016

Date of final enrolment

26/02/2021

Locations

Countries of recruitment

United Kingdom

England

Belgium

France

Germany

Greece

Italy

Poland

Portugal

Study participating centre

Brussels Saint-Luc University Hospital (Cliniques Universitaires Saint-Luc)

Clinical Trial Center (CUSL/CTC)

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Study participating centre

The Northern Lisbon Hospital Center – Santa Maria University Hospital / Faculty of Medicine of University of Lisbon (D. Brito; F. Pinto)

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Athens University Medical School (NKUA)

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Study participating centre

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Study participating centre

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Sponsor information

Organisation

Université catholique de Louvain (Belgium)

ROR

<https://ror.org/02495e989>

Funder(s)

Funder type

Government

Funder Name

European Commission (Horizon 2020 grant)

Alternative Name(s)

European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		20/09/2023	06/10/2023	Yes	No
Protocol article	protocol	01/10/2018	05/06/2020	Yes	No
Protocol file	version 7.0	21/10/2019	11/10/2023	No	No
Statistical Analysis Plan	version 7.0	21/10/2019	11/10/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes