ISRCTN65055502 https://doi.org/10.1186/ISRCTN65055502

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

Registration date
30/10/2015

Overall study status
Completed

Last Edited
11/10/2023

Condition category
Circulatory System

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] 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: β3AR 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 β3AR 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

Study website
http://beta3lvh.eu

Contact information

Type(s)
Scientific

Contact name
Prof Jean-Luc Balligand

Contact details
UCL-FATH Tour Vésale 5th floor
52 Avenue Mounier B1.53.09
Brussels
Belgium
1200

Type(s)
Public

Contact name
Dr Christophe L. Depoix

Contact details
UCL-FATH Tour Vésale 5th floor
52 Avenue Mounier B1.53.09
Brussels
Belgium
1200
+32 (0)2 764 5288
christophe.depoix@uclouvain.be

Additional identifiers

EudraCT/CTIS number
2015-003146-75

IRAS number

ClinicalTrials.gov number
NCT02599480

Secondary identifying numbers
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 β3-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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

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

Pharmaceutical study type(s)
Dose response

Phase
Phase II

Drug/device/biological/vaccine name(s)
Mirabegron

Primary outcome measure
The primary objective is to evaluate the effect of mirabegron (a new β3-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

Secondary outcome measures
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

Overall study start date
01/03/2016

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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
297

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 β3AR 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
Belgium

England

France

Germany

Greece

Italy

Poland

Portugal

United Kingdom

Study participating centre
Brussels Saint-Luc University Hospital (Cliniques Universitaires Saint-Luc)
Clinical Trial Center (CUSL/CTC)
Avenue Hippocrate, 10
Brussels
Belgium
1200

Study participating centre
The Northern Lisbon Hospital Center – Santa Maria University Hospital / Faculty of Medicine of University of Lisbon (D. Brito; F. Pinto)
Av. Prof. Egas Moniz, 1649-028
Lisbon
Portugal
1649-028

Study participating centre
Athens University Medical School (NKUA)
Attikon Hospital
Athens
Greece
115 27

Study participating centre
Center for Cardiovascular Research Berlin (CCR/Charité)
Hessische Str. 3-4
Berlin
Germany
10115

Study participating centre
Department of Heart Diseases at Wroclaw Medical University (UMW)
ul. Rudolfa Weigla 5
Wroclaw
Poland
50-981

Study participating centre
European Clinical Research Infrastructure Network (ECRIN)
Kerpener Str. 62
Cologne
Germany
50937

Study participating centre
Hospital "Papa Giovanni XXIII" (HPG23)
Piazza OMS, 1

Bergamo
Italy
24127

Study participating centre
Nantes University Hospital (CHU Nantes)
1 Place Alexis-Ricordeau
Nantes
France
44000

Study participating centre
University Medical Center Göttingen (UMG-GOE),
Klinik für Kardiologie und Pneumologie
Robert-Koch-Straße 40
Göttingen
Germany
37099

Study participating centre
University of Oxford – Division of Cardiovascular Medicine and Clinical Magnetic Resonance Research
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Zentrum für Klinische Studien Leipzig (ZKS Leipzig)
Härtelstr. 16-18
Leipzig
Germany
04107

Sponsor information

Organisation
Université catholique de Louvain (Belgium)

Sponsor details
Tour Vésale 5th floor
52 Avenue Mounier B1.53.09
Brussels
Belgium
1200
+32 (0)2 764 5260
jean-luc.balligand@uclouvain.be

Sponsor type
University/education

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, Ευρωπαϊκής Επιτροπής, Европейската комисия, Evropské komise, Commission européenne, Choimisiúin Eorpaigh, Europskoj komisiji, Commissione europea, La Commissione europea, Eiropas Komisiju, Europos Komisijos, Európai Bizottságról, Europese Commissie, Komisja Europejska, Comissão Europeia, Comisia Europeană, Európskej komisii, Evropski komisiji, Euroopan komission, Europeiska kommissionen, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Publication and dissemination plan
We intend to publish a paper on the rationale and design of the study in the next few months, then at least 2-3 additional papers on the results at the end of the study
In the meantime, we may communicate about the study at European Society of Cardiology meetings on the design and preliminary results.

Intention to publish date
01/01/2023

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?
Protocol article	protocol	01/10/2018	05/06/2020	Yes	No
Results article		20/09/2023	06/10/2023	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