Summary of the Trial Report
[Synopsis according to ICH E3]

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

BETA3_LVH

Name of Finished Product/Name of Active Substance:

Betmiga/Mirabegron

Indication/Diagnosis: Structural heart disease at high risk for progressive hypertrophic cardiac remodeling at risk of developing HFpEF (heart failure with preserved ejection fraction).

Phase of Development: Phase IIb

EudraCT-Number: 2015-003146-75

Registration-Number:
Clinical Trials.gov identifier: NCT02599480
ISRCTN-Number: ISRCTN65055502

Date of report: 15.02.2023
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Trial start: 12.09.2016
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The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

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2 Name of Finished Product	3 Name of active Ingredient
Betmiga	Mirabegron
Placebo	None

4 Individual study table

Not applicable

5 Title of Study

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 (BETA3_LVH).

The final trial protocol was version final 7.0 as of October 21st, 2019, including the following amendments:

- amendment 01; submitted in January 2017
  - correction of mistakes, more precise description of procedures
  - addition of a new chapter, describing a scientific sub-project for genetic tests regarding heart failure
  - adaptation of the selection criteria to the current guidelines and addition of a selection criterion: „Patients placed in an institution by official or court order"
  - resulting in trial protocol version final 5.0 of 03.11.2016
  - new IMPD (version 3 of 10.10.2016)
- amendment 02; national and VHP submission between November 2017 and January 2018
  - addition of pO2 and pCO2 measurements from venous blood samples for the calculation of nitrosylated haemoglobin
  - specification of the procedures to be followed for premature termination of trial therapy for individual patients
  - addition of a new trial site
  - minor mistakes were corrected
  - resulting in trial protocol version final 6.0 of 31.08.2017
- amendment 03; national and VHP submission between November and December 2019

- extension of the recruitment period to 53 months
- change in reference safety information (SmPC from April 09th, 2019)
- closure of the University of Oxford as recruiting trial site
- resulting in trial protocol version final 7.0 of 21.10.2019

- In addition, there were two non-substantial modifications:

  - adaptation of the trial documents (patient informed consent) after coming into force of the GDPR (nationally submitted between June and October 2018)
  - addition of a flyer for placement in resident cardiology offices (nationally submitted between June and October 2018)

- and one notification regarding COVID-19 measures taken in the BETA3_LVH trial (submitted nationally starting March 2020)

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8 Publications

Pouleur AC, Anker S, Brito D, Brosteanu O, Hasenclever D, Casadei B, Edelmann F, Filippatos G, Gruson D, Ikonomidis I, Lhommel R, Mahmod M, Neubauer S, Persu A, Gerber BL, Piechnik S, Pieske B, Pieske-Kraigher E, Pinto F, Ponikowski P, Senni M, Trochu JN, Van Overstraeten N, Wachter R, Balligand JL. Rationale and design of a multicentre, randomized, placebo-controlled trial of mirabegron, a Beta3-adrenergic receptor agonist on left ventricular mass and diastolic function in patients with structural heart disease Beta3-left ventricular hypertrophy (Beta3-LVH). ESC Heart Fail. 2018 Oct;5(5):830-841. doi: 10.1002/ehf2.12306. Epub 2018 Jun 22. Erratum in: ESC Heart Fail. 2018 Dec;5(6):1199. PMID: 29932311 PMCID: PMC6165933.

9 Studied period (in years)

Date of first enrolment: 12.09.2016

Date of last completed: 16.03.2022

10 Phase of Development

The BETA3_LVH trial was a Phase II b trial using an medicinal product approved for the treatment of a non-cardiovascular disease (overactive bladder disease) in patients presenting with heart failure with preserved ejection fraction (HFpEF). Thus, the IMP was used outside the approved indication.

11 Objectives

Primary objective:

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).

Secondary objectives:

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

12 Methodology

This is a two armed, prospective, randomized, placebo-controlled, multi-centric international phase IIb trial.

Randomisation of patients between verum and placebo was performed centrally via a secure web-based tool using a modified minimisation procedure with stochastic component according to Pocock (1983) in a 1:1 proportion.

Randomisation was balanced according to the following criteria:
- Atrial fibrillation (yes / no)
- Diabetes mellitus (yes / no)
- Trial site

The study is double-blind, and in addition, the two primary endpoints were assessed centrally in respective core labs, using standardized protocols.

To ensure identical analyses of the data relevant for endpoint evaluation, core labs were commissioned with the analyses of data recorded at the trial sites. This included:
- MRI core lab responsible for the analyses regarding a change in left ventricular mass index relevant for the co-primary endpoint.
- ECHO core lab to perform data analyses assessing the diastolic function (E/e') with regards to the co-primary endpoint.
- Central Lab for analysis of samples of BETA3_LVH patients regarding metabolic parameters (fasting glucose, HOMA test, HbA1c, serum lipids) and biomarkers of special interest (Galectin3, GDF15, NT-proBNP, hsTnT).

An Independent Data Safety and Monitoring Board (DSMB) was set-up and met periodically to review the results of the clinical trial, to evaluate any safety issues that aroused during the course of the study and to advise the study investigators on the required course of action.

13 Number of patients (planned and analysed)

Planned number:	296 patients overall (148 patients per treatment arm)
Registered/screened subjects:	380 patients
Recruited subjects	296 patients
Analyzed patients:	296 patients (all patients included in final analysis)
Drop-outs:	35 patients dropped-out before the final visit. However, a statistical model was used which allowed for incorporation of incomplete information

For details see the CONSORT-flow diagram in appendix

14 Diagnosis and main criteria for inclusion

Inclusion criteria:
- Age between 18 and 90 years
- Morphological signs of structural cardiac remodelling by echocardiography, i.e. increased LV mass index (≥95 g/m^2 or higher for female; ≥115 g/m^2 or higher for male subjects) or end-diastolic wall thickness ≥13 mm in at least one wall segment
- Written informed consent

Major exclusion criteria:

- Unstable arterial 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
- Hypertensive patients not under stable therapy according to current guideline algorithm (including stable medication for at least 4 weeks before inclusion)
- Documented ischemic cardiac disease:
  - current angina pectoris or
  - ischemia on stress test or
  - untreated coronary stenosis >50% or
  - history of acute myocardial infarction (AMI) or
  - coronary artery bypass graft (CABG, < than 3 months prior to screening) or
  - percutaneous transluminal coronary angioplasty (PTCA) less than 3 months prior to screening.
- Patients with uncontrolled recurrent persistent and permanent atrial fibrillation (AF) according to AHA/ACC/ESC guidelines (with a heart rate > 100/min, RACE II - (Groenveld et al. 2013). If AF with HR>100/min, the patient may be rescreened after treatment for rate control.
- History of hospitalization for overt heart failure within last 12 months
- History of high degree impulse conduction blocks (> 2nd degree AV block type 2)
- Patients after heart transplantation
- Genetic hypertrophic or dilated cardiomyopathy
- Dysthyroidism
- Severe valvulopathy (less than 1 cm2 aortic valve area, mitral insufficiency of severe grade at Doppler echo)
- Congenital valvulopathies
- Patients with a known history of QT prolongation (QT>450ms) or patients with documented QT prolongation (QT>450 ms) while taking medicinal products known to prolong the QT interval.
- NYHA-class > II
- BMI > 40 kg/m^2
- EF < 50%, regardless of symptoms
- 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 efficiently controlled by CPAP for at least one year before inclusion in the study
- Moderate renal impairment defined as eGFR < 30 ml/min
- Abnormal liver function tests (AST or ALT >2 X upper normal limit or patients with known hepatic impairment defined as Child-Pugh class B or higher)
- Type I diabetes, complicated type II diabetes (i.e., with documented coronary macroangiopathy, cfr exclusion criterion 1 or documented other vascular complication).
- Patients with anemia (male: Hb <130 g/l, female: Hb <120 g/l)
- Patients with bladder outlet obstruction
- Patients using antimuscarinic cholinergic drugs for treatment of OAB
- Current use of digitalis, bupranolol, propranolol, nebivolol (known to interfere with β3AR signalling)
- Patients continuously treated with Sildenafil or other PDE5 inhibitors.

- Current use of antifungal azole derivatives (fluconazole, itraconazole, miconazole, posaconazole, voriconazole) (known inhibitors of CYP3A4, the main metabolizer of mirabegron)
- Current treatment with mirabegron or indication for future treatment with mirabegron due to other indications
- Contraindication for MRI (e.g., defibrillator, ferromagnetic devices or severe claustrophobia, pacemaker - the latter only, if MRI is contraindicated)
- Pregnant or nursing women
- Women of child bearing potential without highly effective contraceptive measures

15 Information on the Test Product

Administration of 50 mg mirabegron once daily per os (Betmiga®, Astellas Pharma) over a period of 12 months.

Batch numbers:

- 15G23/41
- 17I12/26
- 18C16/26
- 19K03/28

16 Duration of Treatment

12 months treatment per patient with an additional follow-up-phone visit at month 13

17 Reference Therapy

Administration of placebo once daily per os over a period of 12 months.

Batch numbers:

- 182050
- 192054
- 192064

18 Criteria for Evaluation

18.1 Efficacy

Two equally ranked, primary endpoints:

- Change in left ventricular mass index (LVMI in g/m^2, defined as left ventricular mass divided by body surface) measured at baseline and 12 months after randomisation.
- 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 endpoints:

- Further MRI endpoints (all measured in the central MRI core lab)
    - Cardiac fibrosis at baseline and at 12 months. Fibrosis is a key pathogenic mechanism of diastolic dysfunction, which is at the origin of HFpEF
    - Left atrial volume index at baseline and at 12 months
    - LV mass index (by cardiac MRI) at 6 months,
    - Diastolic function (E/e') at 6 months;
- Laboratory parameters at baseline and at 3, 6 and 12 months
    - serum biomarkers (Galectin3, GDF15, NT-proBNP, hsTnT)
    - metabolic parameters (fasting glucose, modified HOMA test, HbA1c, serum lipids)
- Maximal exercise capacity (peak VO_2) at baseline and 12 months.

18.2 Safety

Safety endpoints

- Incidence, severity and frequency of adverse and serious adverse events
- Mortality

19 Statistical Methods/analysis procedures

Primary endpoints:

Confirmatory analysis follows the intention to treat principle as close as possible and will be based on the full analysis set.

In each patient, the primary endpoints were to be assessed thrice: at the baseline visit, and at the 6 and 12 months visits. Analyses of both primary endpoints are identically structured:

Mean changes from baseline mean are analysed using a repeated measurement linear mixed model without intercept containing the fixed, categorical effects of

- visit (baseline, 6 months, 12 months),
- treatment (verum / placebo),
- treatment by visit interaction
- Atrial fibrillation (yes / no),
- Diabetes mellitus (yes / no),

as well as a patient-specific, visit random effect (3-dimensional normal with a general unstructured variance covariance matrix).

Secondary endpoints:

All other MRI and echocardiographic endpoints as well as peak VO_2 are analysed along the same lines as the primary endpoints. Time courses of metabolic parameters and specific biomarkers are described.

20 Summary/Conclusion

20.1 Efficacy results

Primary endpoints

The baseline and covariates adjusted differences between mirabegron and placebo in LVMi at 12 months was +1.3 g/m^2 [95% confidence interval (CI): -0.15; 2.74; p=0.079]; and in E/e' at 12 m: -0.15 [95% CI: -0.69; 0.4; p=0.6].

The following figures show the change in primary endpoints over time in the Mirabegron and Placebo groups.

Figure 1a: LVMI:

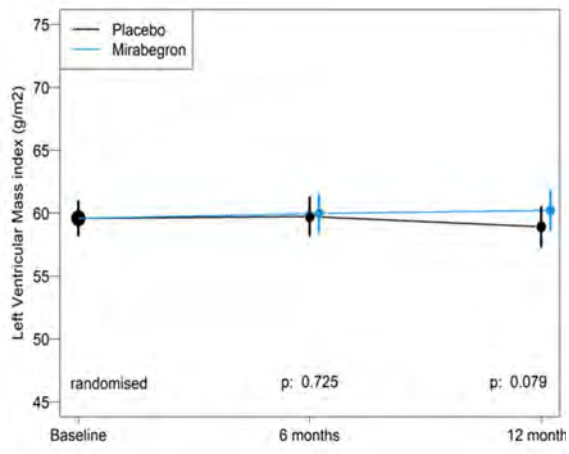
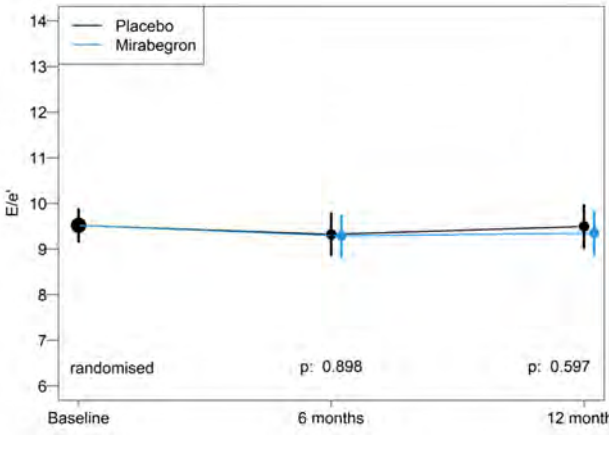


Figure 1b: E/e':



Treatment-specific differences at post-baseline visits in LVMi (Fig 1a) and E/e' (Fig 1b) deduced from the basic linear mixed model (see Methods). As the groups are randomized, the mean at baseline is not estimated separately by arm. P values refer to treatment differences tested against zero.

Secondary endpoints

The following figure shows the comparative effect of mirabegron and placebo on the main pre-specified secondary endpoints:

Figure 2: treatment effect for pre-specified secondary endpoints

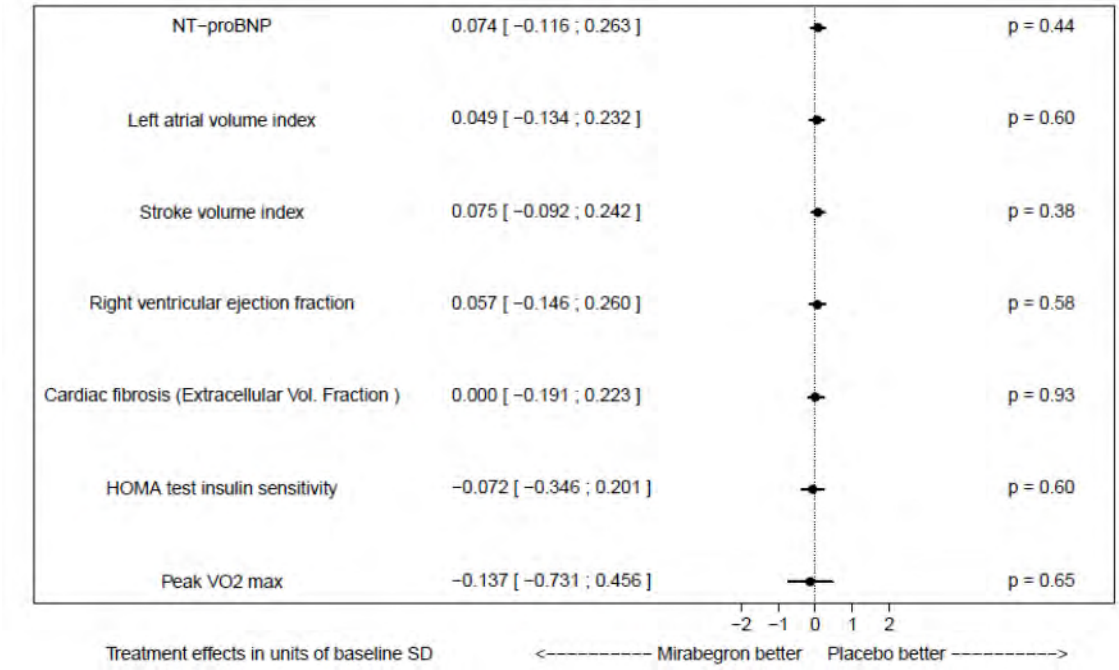


Figure 2 shows the model estimated treatment effect at 12 months of mirabegron versus placebo for the seven pre-specified key secondary outcomes. Treatment effects with 95% confidence intervals are provided using the pooled baseline standard deviation as unit, allowing to show all endpoints on the same effect size scale.

20.2 Safety results

A total of 428 adverse events (AEs) were recorded, 213 in the mirabegron and 215 in the placebo arm, affecting a total of 170 patients (82 in the mirabegron and 88 in the placebo group) (Table 1).

	Mirabegron (n=147)		**Placebo (n=149)**	
	Patients with AE	Total AEs	Patients with AE	Total AEs
Any AE	82	213	88	215
Of which SAE	19	31	22	30
Any AE leading to permanent treatment discontinuation	7	11	9	17
Any AE leading to treatment interruption	9	16	9	10
Arrhythmia (AF, Flutter)	7	17	4	3
High blood pressure (systolic or diastolic)	34	21	29	19
Renal insufficiency (eGFR<30ml/min)	0	0	1	1
Liver enzymes elevation (ALT or AST >2 xULN)	6	5	2	2

Table 1: Description of adverse events

A total of 61 serious AEs were reported, 31 in the mirabegron group (in 19 patients), and 30 in the placebo group (in 22 patients). Of them, 18 events were considered to be related to the study medication by two independent evaluators, 12 out of 9 patients in the mirabegron group (5 increased blood pressure, 2 elevated ALT, 3 paroxysmal atrial fibrillation in one patient, 2 paroxysmal atrial flutter in one patient); and 6 out of 6 patients in the placebo group (3 increased blood pressure, 1 abnormal glomerular filtration rate, 1 atrial flutter, 1 atrial fibrillation). In total, 4 SUSARs in 3 patients were reported in the BETA3_LVH-trial. However, since SUSARs are only reported to the competent authority, if they occur in the verum treatment arm, these cases (all placebo-cases) were neither reported, nor listed in the line listings/summary tabulations.

Study medication was discontinued because of an SAE in 3 patients in the mirabegron group (granular cell tumour, prostate cancer, ALT increase) and 4 patients in the placebo group (joint arthroplasty, anaemia and sepsis in one patient; increased blood pressure; coronary artery disease; myocardial infarction). There were no deaths reported during the trial.

20.3 Conclusions

Mirabegron therapy was safe, but had no effect on LV myocardial mass or diastolic function over a 12-month follow-up in patients with structural heart disease presenting without or only mild cardiac symptoms (pre-HF patients (Stage B), according to the Universal definition of HF; Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021 Mar;23(3):352-380).As current guidelines emphasize the

need to identify new treatment strategies to prevent pre-HF patients from developing overt HF (Stage C), higher doses of mirabegron or other more potent beta3AR agonists deserve to be tested in future trials.

21 Appendix

21.1 Abbreviations

AE	Adverse Event
AF	atrial fibrillation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body mass index
COPD	Chronic Obstructive Pulmonary Disease
DSMB	Data Safety Monitoring Board
EF	Ejection Fraction
eGFR	estimated glomerular filtration rate (MDRD formula)
Hb	Hemoglobin
HFpEF	Heart Failure with preserved Ejection Fraction
LLT	Lower Level Term
LVMI	Left ventricular mass index
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
OAB	Over-Active Bladder
PT	Preferred Term
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper level normal

21.2 CONSORT Flow Diagram