Trial Protocol

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

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Synopsis

Title of the trial	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
Indication	Structural heart disease at high risk for progressive hypertrophic cardiac remodeling at risk of developing HFpEF (heart failure with preserved ejection fraction).
Primary goal of the trial / primary end point	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). <u>Two equally ranked, primary endpoints:</u> • 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 goals of the trial / secondary end points	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). <u>Secondary endpoints:</u> • 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. This parameter determines diastolic filling (and was shown to predict treatment efficacy in HFpEF in the J-DHF trial (Yamamoto et al. 2013)) - 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 VO2) at baselineand 12 months.

	• Safety endpoints - Incidence, severity and frequency of adverse and serious adverse events - Mortality
Trial design	Two armed, prospective, randomized, placebo-controlled, multi-centric international phase IIb trial
Trial population	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 (Ponikowski et al. 2016)) or end-diastolic wall thickness ≥13 mm in at least one wall segment • Written informed consent 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. 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 (Mancia et al. 2013) (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 (Dixon et al. 2005) (with a heart rate > 100/min, RACE II - (Groenveld et al. 2013, 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) (National Diabetes Education Initiative - NDEI). • 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) • Note: patients are allowed to take a β(1-2)-blocker, other than the drugs listed above (for explanation, see chapter **Erreur ! Source du renvoi introuvable.**). • 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 (Clinical Trial Facilitation Group (CTFG) 9/15/2014): - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) - intrauterine device (IUD)

	- intrauterine hormone-releasing system (IUS) - bilateral tubal occlusion - vasectomised partner - sexual abstinence (only if in agreement with the preferred and usual lifestyle of the subject) while participating in the trial. There are no known interactions of the trial medication and hormone-based methods of contraception. In particular, no clinically relevant interactions have been observed when mirabegron was co-administered with therapeutic doses of a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. • Participation in any other interventional trial • Patients unable to give informed consent (people under legal guardianship) • Patients placed in an institution by official or court order • Contraindication to mirabegron (e.g. hypersensitivity) or any other components of the trial medication
Sample size	296 patients overall (148 patients per treatment arm) will be randomised
Therapy	Experimental group: Administration of 50 mg mirabegron once daily per os (Betmiga®, Astellas Pharma) over a period of 12 months. Control group: Administration of placebo once daily per os over a period of 12 months. Verum and placebo will be manufactured by: Pharmacy of the University Hospital Leipzig Liebigstr. 20 D-04103 Leipzig
Biometry	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 will be assessed thrice: at the baseline visit, and at the 6 months and 12 months visits. Analyses of both primary endpoints are identically structured: Mean changes from baseline mean will be 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 VO2 will be analysed along the same lines as the primary endpoints. Time courses of metabolic parameters and specific biomarkers will be described. Adverse and serious adverse events will be compared by chi-square tests. Odds ratios with 95% confidence intervals will be provided.
Trial Duration	Individual treatment period: 12 months treatment per patient with an additional follow-up-phone visit at month 13 Trial: • First patient in: April 2016 • Patient-screening and recruitment: 33 months • Last patient out (planned): December 2019 • Final analysis (planned) December 2020