Final report AEMPS

• Study title: **β3 adrenergic agoniSt Treatment in Chronic Pulmonary HypERtEnsion Secondary to Heart Failure: a Randomized Placebo-Controlled Phase 2 Clinical Trial**

• Name of test drug/investigational product: Mirabegron

• Indication studied: Combined pre and postcapillary pulmonary hypertension.

• Name of the sponsor: Fundació Clínic pera a la Recerca Biomèdica

• Protocol identification (code or number): Nº EudraCT: 2016-002949-32

• Development phase of study: II

• Study initiation date (first patient enrolled): 21.Jun.2017

• Date last patient in: 21.Dec. 2020

• Study completion date (last patient completed): 4.June. 2021

• Date of end of the study: 4. June. 2021

• Name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer: Hospital Clínic Barcelona.

• Name of company/sponsor signatory (the person responsible for the study report within the company/sponsor. The name, telephone number and fax number of the company/sponsor contact persons for questions arising during review of the study report should be indicated on this page or in the letter of application.): Ana García Álvarez, anagarci@clinic.cat, 635264584.

• Statement indicating whether the study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents: The study was performed in compliance with GCP.

• Date of the report: 31.OCT.2022.

Synopsis:

Background and Aims: Pulmonary hypertension (PH) associated with left heart disease is an increasingly prevalent problem, orphan of targeted therapies, and related to a poor prognosis, particularly when pre and postcapillary PH combine. The current study aimed to determine whether treatment with the selective β3 adrenoreceptor agonist mirabegron improves outcomes in patients with combined pre and postcapillary PH (CpcPH).

Methods and Results: The β3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure (SPHERE-HF) trial is a multicenter, randomized, parallel, placebo-controlled clinical trial that enrolled stable patients with CpcPH associated with symptomatic HF. A total of 80 patients were assigned to receive mirabegron (50 mg daily, titrated till 200 mg daily, n=39) or placebo (n=41) for 16 weeks. Of them, 66 patients successfully completed the study protocol. The primary endpoint was the change in pulmonary vascular resistance (PVR) on right heart catheterization. Secondary outcomes included the change in right ventricular (RV) ejection fraction by cardiac magnetic resonance or computed tomography, other hemodynamic variables, functional class, and quality of life. The trial was negative for the primary outcome (placebo-corrected mean difference of 0.62 Wood units, 95%CI -0.38, 1.61 WU, p=0.218). Patients receiving mirabegron presented a significant improvement in RV ejection fraction as compared to placebo (placebo-corrected mean difference of 3.0%, 95%CI 0.4, 5.7%, p=0.026), without significant differences in other pre-specified secondary outcomes.

Conclusions: SPHERE-HF is the first clinical trial to assess the potential benefit of β3 adrenergic agonists in PH. The trial did not met the primary outcome since mirabegron did not reduce PVR in CpcPH. On pre-specified secondary outcomes, a significant improvement in RV ejection fraction was found, without differences in functional class or quality of life.

List of abbreviations

AE: Adverse events

β3AR: B3-adrenergic receptors

CCT: Cardiac computed tomography

CMR: cardiac magnetic resonance

HF: Heart failure

HFpEF: Heart failure with preserved ejection fraction

HFrEF: Heart failure with reduced ejection fraction

PH: Pulmonary hypertension

Ethics

The study and an amendment were reviewed by the Institutional Review Board in Hospital Clínic Barcelona.

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Informed consent was obtained previously to randomization. A copy is provided in Appendix 1.

Investigators and study administrative structure

Coordinator: Dra. Ana García Álvarez

Promotor center: Fundació Clínic per a la Recerca Biomèdica.

Co-promotor center: Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC)

Steering committee:

PI CNIC: Dr. Borja Ibáñez Co-IP: Dr. Valentín Fuster

PI Hospital Clínic: Dra. Ana García Álvarez

PI Hospital de la Santa Creu i Sant Pau: Dra. Eulàlia Roig

PI 12 de Octubre: Dr. Juan Delgado

PI Puerta de Hierro: Dr. Javier Segovia

Data safety monitoring board: Dr. Rodrigo Fernandez-Jimenez, Dr. Juan Manuel García-Ruiz, Dr. Xavier Roselló.

Statisticians: Albert Cobos. Universitat de Barcelona.

CRO: Anagram

List of investigators:

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Responsible statistician: Albert Cobos, Universitat de Barcelona.

Introduction:

Pulmonary hypertension (PH) commonly complicates heart failure (HF) and confers a bad prognosis[1,2]. Up to two thirds of patients with HF with both reduced (HFrEF) or preserved ejection fraction (HFpEF) develop PH[3–5]. Of them, approximately 13% progress to combined pre- and post-capillary PH (CpcPH), characterized by higher pulmonary vascular resistance (PVR), more severe pulmonary vascular remodeling and worse prognosis than isolated post-capillary PH[3]. Right ventricular (RV) function is a well-recognized prognostic factor in PH associated with left heart disease (LHD), with an impact even greater than the severity of the increase in PVR[1]. Currently there are not specific pharmacological therapies approved for patients with CpcPH either to improve pulmonary hemodynamics or RV adaptation[6]. Beta-3 adrenoreceptors (β3AR) are expressed in the human myocardium[7] and vessels[8] and have been described to be upregulated in LHD[7]. Their stimulation or overexpression has been shown to cause vasodilatation[9,10] and prevention of cardiac remodeling in experimental animal models[11–13]. In addition, prior experimental research has demonstrated the presence of mRNA expression of hB3AR in human pulmonary arteries and has shown that treatment with β3AR agonists produced a beneficial effect on pulmonary hemodynamics and RV performance, associated with an attenuation in pulmonary vascular proliferation in a swine model of chronic postcapillary PH[14]. The selective oral β3AR agonist mirabegron is currently approved for the treatment of overactive bladder syndrome and has demonstrated a good safety profile in healthy subjects and patients, both suffering from the urinary condition[15–17] or HFrEF[18]. The potential efficacy of treatment with β3AR agonists on patients affected by PH has never been evaluated. On the basis of these considerations, the B3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure (SPHERE-HF) trial was set up to evaluate the efficacy and safety of the selective B3AR agonist mirabegron in patients with CpcPH. Our hypothesis was that treatment with mirabegron in patients with CpcPH would result in a beneficial effect due to: 1) a reduction in PVR, 2) an increase in RV performance, and 3) improvement in clinical status without an increase in severe adverse events.

Study objectives

The primary outcome was the change from baseline to week 16 in PVR on RHC, calculated in Wood units, as the difference between mean PAP (mmHg) and PAWP (mmHg), divided by the cardiac output (L/min). Pre-specified secondary outcomes were the change from baseline in: RV ejection fraction assessed by advanced imaging (CMR or CCT), NYHA functional class, 6-minute walk distance, dyspnea Borg scale score, quality of life evaluated by the Kansas City

Cardiomyopathy Questionnaire overall summary score, mean PAP, transpulmonary gradient, diastolic gradient, cardiac output, and NTproBNP. Safety measures included HF decompensation, death, urgent heart transplantation, adverse events and adverse drug reactions, as well as monitorization of heart rate and the QTc interval on ECG. An independent data safety monitoring board reviewed all major events and determined the potential relationship with study medication, according to standard operational procedures. An imaging core-lab centered in Centro Nacional de Investigaciones Cardiovasculares (CNIC) measured all acquired images (echocardiograms, CMR and CCT) in a completely blinded fashion and reported directly to the external statistics board.

Investigational plan

The β3 Adrenergic Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure (SPHERE -HF) trial was a Phase II double-blind multicenter, with balanced randomization (1:1), placebo-controlled, parallel-group clinical trial conducted in Spain (5 sites). The study received ethical approval from regional and national health service research ethics committees and was conducted in accordance with the principles of good clinical practice. All patients provided written informed consent before randomization. The Hospital Clínic de Barcelona coordinated the trial in collaboration with the Centro Nacional de Investigaciones Cardiovasculares (CNIC). An independent data safety monitoring board reviewed safety data every 6 months throughout the trial. This trial was registered at ClinicalTrials.gov NCT02775539 and EudraCT: 2016-002949-32. Details of the trial design have been previously reported[19].

Participants

Patients with PH associated with HF were screened for possible inclusion. Eligible participants were adults aged 18 or over with symptomatic HF (NYHA functional class II-III) and secondary CpcPH who were on optimized evidence-based pharmacological treatment and stable clinical condition during the 30 days preceding recruitment. Inclusion and exclusion criteria are presented on **Table 1**. The exclusion criteria of QTc interval on ECG >430 ms in men and >450 ms in women, that had been established as a general safety standard, was modified by an amendment to QTc >480 ms, based on the high percentage of patients with CpcPH who presented this exclusion criteria at baseline and the absence of data suggesting that mirabegron at the doses used could significantly increase QTc.

Manufacturing of study medication

Manufacturing of mirabegron and placebo was carried out at the Hospital Clínic Pharmacy department. The excipient for placebo capsules (mixture of microcrystalline cellulose and colloidal silica) was received from the manufacturer (Fagron Iberica S.A.U, Terrassa, Spain) and included in capsules. Similarly, mirabegron pills was bought from Astellas Pharma (Chuo, Tokyo, Japan), taken out of the blisters, and automatically encapsulated (a single pill into a capsule). Immediately, capsules containing mirabegron or excipient (exactly the same appearance and taste) were introduced in polyethylene bottles (30 capsules each), labeled as study medication with the batch number and expiration, and kept in the clinical trials area in conservation conditions (atmosphere temperature <25ºC). Labeled was done in a blinded manner to guarantee masking of patients and physicians. Extra tablets were given at each clinical visit. Therapeutic compliance was evaluated by counting empty blisters and remaining tablets.

Randomization and blinding

Patients were randomly allocated (1:1) to mirabegron or placebo using randomly selected block sizes stratified by center using the Blockrand package (R Foundation). Generation of the randomization list and allocation concealment were done by statisticians who were independent from researchers and the people involved in the implementation of assignments. The randomization list was provided exclusively to the pharmacy department, which was responsible for the preparation of medication kits by identifying them with a unique sequential number for the entire study and provide them to the centers. Researchers assigned medication kits in a sequential order and recorded the kit number provided to each patient in the data collection system.

Procedures

Patients underwent the following baseline procedures and assessments within 4 weeks before random allocation: demographic and medical history data collection; physical examination (including blood pressure, heart rate, and pulse oxymetry); NYHA functional class; blood sample analysis including NT-proBNP; ECG; echocardiography; right heart catheterization (RHC); 6-minute walking test, and a cardiac magnetic resonance (CMR) or a cardiac computed tomography (CCT). CMR was used preferably but in patients with severe claustrophobia or cardiac devices, a dedicated CCT examination was performed instead to measure RV volumes and function. The protocol for the RHC was previously written and standardized in all

participating hospitals. Briefly, the procedure was performed in a supine position with patients breathing mostly room air or supplementary oxygen when needed through a venturi mask with a fixed FiO_2. Zero reference level was stablished at mid thoracic level, at the intersection of the frontal plane at the mid thoracic level, and the transverse plane at the level of fourth anterior intercostal space. Determination of all pressure values was an averaged over 3-5 respiratory cycles (continuous registry). Systemic blood pressure was firstly measured, followed by the measurement of systolic, diastolic and mean pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP, including "v" wave when existed) and right atrial pressure. When patients were in atrial fibrillation a longer stretch of the record was analyzed. Determination of cardiac output was made by thermodilution at least 3 times without a difference greater than 10%. Finally, a sample from the pulmonary artery was drawn to measure PvO2 and SvO2. A complete description of the examinations, hemodynamic and imaging protocols have been previously published[19].

Eligible patients were randomized to receive mirabegron (50 mg) or placebo once daily on Visit 0, started study medication on Visit 1 (during the 5 days after randomization), and were reviewed one week later in a safety visit (Visit 2), all in a blinded fashion. Thereafter, medication dose was uptitrated every 2 weeks for 8 weeks (up to a maximum of 200mg daily) based on patients' blood pressure, heart rate, QTc interval, blood analysis and clinical status assessed at each visit, and then maintained for another 8 weeks. Once finished the 16-week period under treatment, patients underwent the same study examinations performed at baseline and stopped the study medication. A final security monitoring visit took place 30 days after the last study medication dose, following clinical trials regulation. **Figure 1** shows the scheme of the study conduct and procedures.

Discussion of Study Design, including the Choice of Control Groups

The specific control chosen was placebo concurrent control (as there is no treatment approved for this indication).

The present study was designed and developed with a robust methodology (multicenter, randomized, double-blind clinical trial), however we can point out some limitations. It included a heterogeneous cohort of patients with both HFrEF and HFpEF. Despite being aware of the differences in the physiopathology of both entities, we prioritized the fact that all patients had CpcPH, as we hypothesized that the main effect exerted by mirabegron would be the reduction of PVR. Considering that the beneficial effect might be greater at the myocardial level, it would possibly have been more appropriate to focus on a single HF phenotype. Measurement of

cardiac output by right heart catheterization, needed for PVR calculation, was done by thermodilution, which may be inaccurate in patients with severe tricuspid regurgitation (present in 10 patients at baseline and 11 at 16-week follow-up). This fact may explain, at least partially, the discordance observed between the increase in RV ejection fraction and the absence of a significant increase in cardiac output. Indeed, in the subpopulation with available advanced imaging, cardiac output by CMR did increase in patients receiving mirabegron (though differences did not reach significance as compared to placebo). Two thirds of patients had atrial fibrillation at baseline, and we cannot exclude a lower benefit in these patients compared to those in sinus rhythm, as has been observed with the use of betablockers in HFrEF[53], although the results of the exploratory analysis do not point in this direction. Also, approximately one third had PH associated with corrected valve disease, subgroup probably representing long evolution chronic PH, especially refractory to treatment. Another limitation is associated with the baseline observation carried forward approach used to deal with missing data in the ITT population, which assumes no changes in patients receiving placebo or mirabegron. Nevertheless, no differences were observed in the results obtained in the PP or the ITT population.

Selection of Study Population

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Written informed consent.	Non-coronary cardiac surgery (e.g. valvular surgery) or non-coronary structural percutaneous procedure (e.g. percutaneous mitral reparation) within the 12 months preceding recruitment or scheduled.
≥18 years-old.	Myocardial infarction or coronary revascularization within the 3 months preceding recruitment.

Inclusion criteria	Exclusion criteria
HF with reduced, intermediate or preserved LVEF, according to the definition of the European Society of Cardiology guidelines[6].	CRT implantation within the 6 months preceding recruitment.
Combined pre- and postcapillary PH determined by RHC showing the following: ▪ PAWP or LVEDP ≥15 mmHg. ▪ Mean PAP ≥25 mmHg; and: • PVR ≥3 WU and/or diastolic gradient ≥7 mmHg, or • Transpulmonary gradient ≥12 mmHg.	Sinus tachycardia or uncontrolled atrial fibrillation (HR >100 bpm).
NYHA functional class II-III.	Uncontrolled systemic hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg) or symptomatic hypotension (systolic BP <90 mmHg).
On optimized evidence-based pharmacological treatment.	Diagnosis of infiltrative cardiomyopathy.
Stable clinical condition defined as no changes in therapeutic regimen for HF or hospitalization in the 30 days preceding recruitment and no current plan for changing therapy.	Pre-menopausal women who have not undergone total hysterectomy.
	Expected survival <1 year due to a disease other than HF.
	Severe renal failure (GFR<30 mL/min/1.73 m^2).

	Severe hepatic impairment (transaminase elevation>3 times ULN).
	Prolonged cQT interval on the ECG > 480 ms.
	Concomitant use with specific pulmonary vasodilators (sildenafil, bosentan, macicentan, riociguat or other endothelin receptor blockers, phosphodiesterase 5 inhibitors or guanylate cyclase stimulators).
	Treatment with digoxin, flecainide, propafenone, dabigatran, tricyclic antidepressants or other CYP2D6 inhibitors (other than beta-blockers).
	Severe COPD (FEV1/FVC ratio <0.7 together with FEV1<50% predicted value).
	Severe restrictive lung disease (TLC <50%).
	Participation in another clinical trial.
	Known allergy to mirabegron or any of the excipients.

Removal of patients from therapy: none.

Treatments:

Treatment administered: mirabegron vs. placebo titrated till 200 mg/day orally.

Investigational product: Manufacturing of mirabegron and placebo was carried out at the Hospital Clínic Pharmacy department. The excipient for placebo capsules (mixture of microcrystalline cellulose and colloidal silica) was received from the manufacturer (Fagron Iberica S.A.U, Terrassa, Spain) and included in capsules. Similarly, mirabegron pills was bought

from Astellas Pharma (Chuo, Tokyo, Japan), taken out of the blisters, and automatically encapsulated (a single pill into a capsule). Immediately, capsules containing mirabegron or excipient (exactly the same appearance and taste) were introduced in polyethylene bottles (30 capsules each), labeled as study medication with the batch number and expiration, and kept in the clinical trials area in conservation conditions (atmosphere temperature <25ºC). Labeled was done in a blinded manner to guarantee masking of patients and physicians. Extra tablets were given at each clinical visit. Therapeutic compliance was evaluated by counting empty blisters and remaining tablets.

Method of assigning patients to treatment groups

Patients were randomly allocated (1:1) to mirabegron or placebo using randomly selected block sizes stratified by center using the Blockrand package (R Foundation). Generation of the randomization list and allocation concealment were done by statisticians who were independent from researchers and the people involved in the implementation of assignments. The randomization list was provided exclusively to the pharmacy department, which was responsible for the preparation of medication kits by identifying them with a unique sequential number for the entire study and provide them to the centers. Researchers assigned medication kits in a sequential order and recorded the kit number provided to each patient in the data collection system.

Selection of doses in the study

The dose was based on several phase 2 and phase 3 randomized clinical trials (Malik, van Gelderen et al 201225; Chapple, Amarenco et al. 201326; Chapple, Dvorak et al 201327; Chapple, Kaplan et al 201328, Hershorn, Barkin et al 201329; Khullar, Amarenco et al 201330; Nitti, Auerback et al 2013)31 have already evaluated the safety of RB3A agonists in healthy subjects and patients with overactive bladder, demonstrating a good safety profile.

Selection and timing of dose for each patient.

Medication dose is titrated every 2 weeks for 8 weeks (visits 3, 4, and 5) based on patients' monitoring of blood pressure, heart rate, QTc interval, blood analysis,and clinical status assessed at that visit, according to the following algorithm:

Clinical assessment	Recommended action
Normal blood pressure (systolic BP ≥95 and ≤135mmHg) **AND** HR ≤90bpm **AND** cQT interval* <430ms in male or <450ms in female **AND** blood analysis within normality **AND** patient asymptomatic	Uptitrate study medication in 50mg/day.
If the patient develops any of the following: significant hypotension (systolic BP <80mmHg) or hypertension (systolic BP >145mmHg) **OR** tachycardia (HR>100bpm) **OR** prolonged cQT interval* (>430ms in male or >450ms in female) **OR** worsening of renal function/transaminase elevation on blood analysis **OR** symptoms associated with medication	Reduce or stop study medication dose
If the patient presents with mild hypotension (systolic BP≥80 y <90mmHg) **OR** mild hypertension (systolic BP >135 y ≤145mmHg) **AND/OR** HR 90-100bpm (with a cQT interval* <430ms in male and <450ms in female) **AND** blood analysis is within normality	Maintain study medication dose

Blinding:

Labeled was done in a blinded manner to guarantee masking of patients and physicians. The randomization list was provided exclusively to the pharmacy department, which was responsible for the preparation of medication kits by identifying them with a unique sequential number for the entire study and provide them to the centers. Researchers assigned medication kits in a sequential order and recorded the kit number provided to each patient in the data collection system.

Prior and concomitant therapy:

Patients had to be on optimized evidence-based pharmacological treatment and stable clinical condition during the 30 days preceding recruitment. Digoxin was not accepted, so it was retired previous to randomization.

Treatment compliance

Extra tablets were given at each clinical visit. Therapeutic compliance was evaluated by counting empty blisters and remaining tablets.

Efficacy and Safety Variables

Efficacy and safety measurements assessed and flow chart

	V0-V1	V2	V3	V4	V5	V6	V7	V8	V9
Informed consent	x								
Inclusion/exclusion criteria	x								
Demographic variables, prior medical history and medication	x								
Anamnesis	x	x	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x	x	x
Laboratory	x		x	x	x	x		x	
ECG	x	x	x	x	x	x	x	x	x
Kansas City Cardiomyopathy Questionnaire	x							x	
Echocardiogram	x							x	
Right heart catheterization	x							x	
NT-proBNP	x							x	
6-minute walking test	x							x	
CMR	x							x	

Primary efficacy variable(s)

The primary outcome was the change from baseline to week 16 in PVR on RHC, calculated in Wood units, as the difference between mean PAP (mmHg) and PAWP (mmHg), divided by the cardiac output (L/min). Pre-specified secondary outcomes were the change from baseline in: RV ejection fraction assessed by advanced imaging (CMR or CCT), NYHA functional class, 6-minute walk distance, dyspnea Borg scale score, quality of life evaluated by the Kansas City Cardiomyopathy Questionnaire overall summary score, mean PAP, transpulmonary gradient, diastolic gradient, cardiac output, and NTproBNP. Safety measures included HF decompensation, death, urgent heart transplantation, adverse events and adverse drug reactions, as well as monitorization of heart rate and the QTc interval on ECG. An independent data safety monitoring board reviewed all major events and determined the potential relationship with study medication, according to standard operational procedures. An imaging core-lab centered in Centro Nacional de Investigaciones Cardiovasculares (CNIC) measured all acquired images (echocardiograms, CMR and CCT) in a completely blinded fashion and reported directly to the external statistics board.

Drug concentration measurements: not performed.

Data Quality Assurance.

An independent CRO monitored each of the visits and patients to ensure the quality of the data.

Statistical Methods Planned in the Protocol and Determination of Sample Size

Determination of sample size

As described previously, assuming a standard deviation of 3.2 WU (based in a population with CpcPH) [20] and a correlation between baseline and 16-week measurement of 0.6, a sample size of 31 subjects per group was required to detect a placebo-adjusted difference of 2.1 WU, with a power of 80% and a 2-sided significance level of 5%. Anticipating a 20% dropout rate, the estimated number of patients needed was 80. Calculations were made using the power.t.test function available in R software (R Foundation, Vienna, Austria).

Statistical and analytical plans

The following analysis populations were predefined: intention to treat (ITT) population (all randomized patients); per protocol (PP) population (patients from the ITT who have the primary outcome measured at 16 weeks and who took at least 80% of all medication doses); and the safety population (all patients who took at least 1 dose of the assigned treatment).

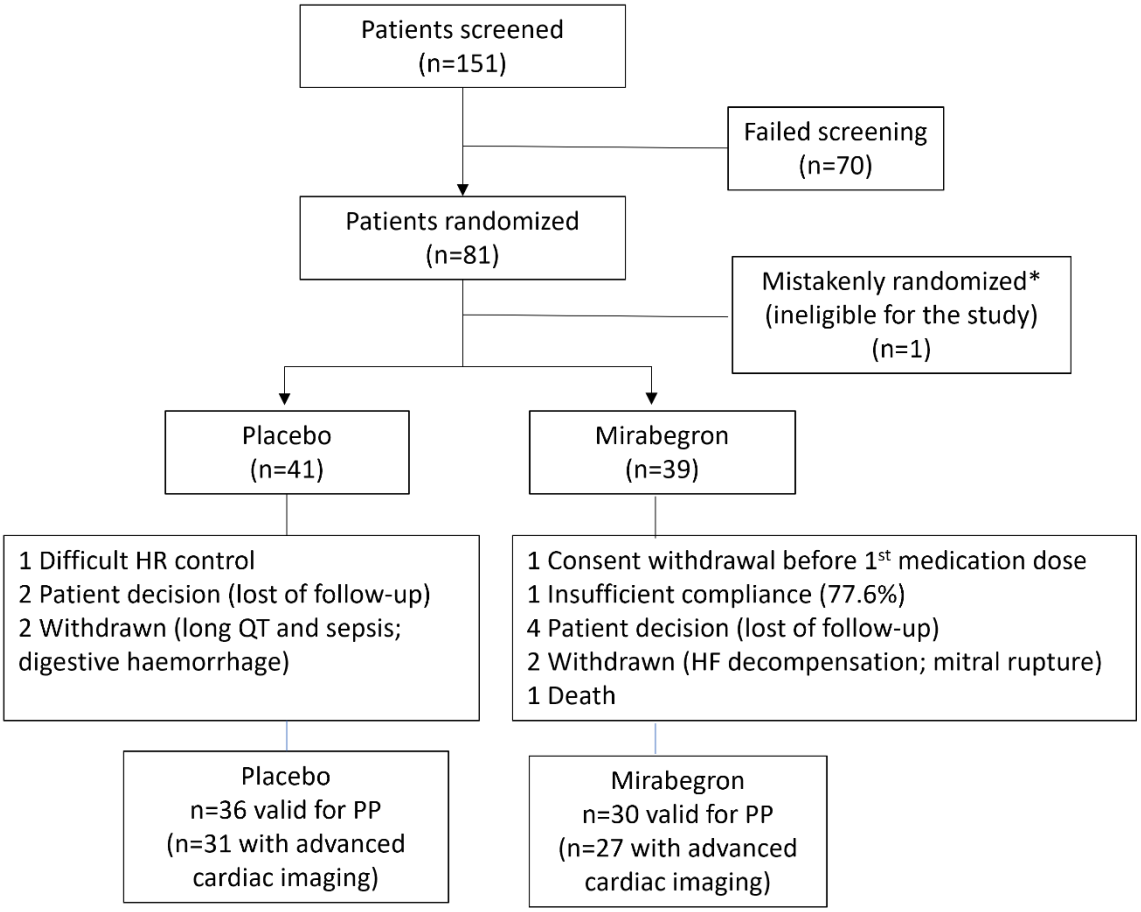
As preestablished in the statistical analysis plan (and previously published[19]), due to the nature of the trial (proof-of-concept) and the selected primary event (PVR on RHC), the primary analysis was performed in the PP population, with supportive analysis in patients on the ITT population. For the ITT population, missing values in the final measure of the primary outcome were replaced by the baseline value (last observation carried forward). The treatment effect on the primary and pre-specified secondary outcomes was analyzed using an ANCOVA model that included the baseline value, treatment, and baseline x treatment interaction. Interaction term was removed if the Wald test was not statistically significant ($p>0.10$). The center was not included in the model due to small center sizes[21]. Model conditions were investigated in all cases (normality of residuals by Shapiro-Wilk test and the presence of observations with influence by graphical methods). In case of deviations from normality or observations with influence, the change from baseline to final measure (delta) was analyzed by randomization test and bootstrapping (9999 replicates), as implemented in the boot.t.test function of the R MKinfer package. In case of NYHA functional class, logistic regression instead of ANCOVA was used. In addition, patients were analyzed by protocol-prespecified subgroups according to left ventricular ejection fraction (<40% vs. ≥40%) and the maximum tolerated dose (mg/dl). Safety analyses were performed descriptively in the safety population. Data are presented as mean±SD or median (1^{st}-3^{rd} quartile) as corresponding. $P<0.05$ was considered as statistically significant. All statistical analysis were undertaken using R package (Vienna, Austria).

Changes in the Conduct of the Study or Planned Analyses: None.

STUDY PATIENTS

Disposition of Patients

Of the 151 patients screened from June 2017 to December 2020, 81 were initially considered eligible for randomization (**Figure**). One patient was excluded after randomization because a lung ventilation-perfusion scan revealed a segmental perfusion defect raising doubts about the potential thromboembolic origin of PH. Of the 80 patients who were included in the ITT population, 67 underwent a second right heart catheterization at 16 weeks and all of them but one achieved at least 80% of therapeutic compliance, so these 66 patients composed the PP population (30 allocated to mirabegron and 36 to placebo). Reasons for withdrawal are summarized in **Figure**.



Results

Demographic and clinical characteristics were well balanced between treatment groups at baseline (**Table 2**). Overall, nearly two thirds of the patients had HFpEF and non-ischemic etiology. About half of the patients had marked limitation of physical activity (NYHA functional class III). Approximately one third (n=19) had previous non-coronary cardiac surgery (aortic and/or mitral valve surgery in 18 patients, and septal myectomy in one) and no patient had severe degenerative valve disease at inclusion. In concordance with the study protocol, patients were receiving state-of-the-art medical and/or device therapy at baseline. In HFpEF, optimized evidence-based pharmacological treatment was focused to the optimal treatment of comorbidities (hypertension, diabetes, heart rate control in the case of atrial fibrillation) and hypervolemia with the use of diuretics. Most patients were treated with betablockers, being selective beta-1 blockers the majority (bisoprolol (n=32, 48%), carvedilol (n=10, 15% of patients),

atenolol (n=5; 7.5% of patients), nebivolol (n=1, 1.5%), and sotalol (n=1, 1.5%). Median therapeutic compliance was 100% of prescribed doses in both groups and median achieved dose was 150 mg in the mirabegron and 125 mg in the placebo group. Of the 66 patients who constituted the PP cohort (with pre-post evaluation of the primary outcome), 58 also had pre-post evaluable advanced cardiac imaging. At baseline, all except two patients underwent CMR (n=42) or CCT (n=22), whereas all but other two had CMR or CCT performed at 16-week follow-up (n=37 and n=27, respectively). Reasons for not performing advanced imaging in these four patients were technical problems (n=3) and patient fragility due to recent hospital admission (n=1). In another four cases, images were considered to be of insufficient quality to be evaluable by the Imaging Core Lab.

Table 2: Baseline demographic and clinical characteristics according to treatment allocation.

	Mirabegron (n=30)	Placebo (n=36)
Age (years)	69.7±9.2	64.8±10.6
Male sex, n (%)	12 (40.0%)	17 (47.2%)
Diabetes mellitus, n (%)	14 (46.7%)	18 (50.0%)
Atrial fibrillation, n (%)	22 (73.3%)	28 (77.8%)
Cardiopathy - Ischemic, n (%) - Non-ischemic, n (%)	 9 (30.0%) 21 (70%)	 10 (27.8%) 26 (72.2%)
HFpEF n (%)	21 (70%)	26 (72.2%)
Left ventricular ejection fraction (%)	50.7 ±14.5	51.7±15.6
NYHA functional class, n (%) II III	 14 (46.7%) 16 (53.3%)	 23 (63.9%) 13 (36.1%)
Previous non-coronary cardiac surgery, n (%)	9 (30.0%)	10 (27.8%)
Pacemaker, n (%)	2 (6.7%)	4 (11.1%)
Cardiac resynchronization therapy, n (%)	2 (6.7%)	0 (0.0%)
Defibrillator, n (%)	7 (23.3%)	11 (30.6%)
Betablockers, n (%)	22 (73.3%)	27 (75%)
ACEI, A2RB or ARNI, n (%)	22 (73.3%)	24 (66.6%)
Mineralocorticoid receptor antagonists, n (%)	14 (46.6%)	22 (61.1%)
Loop diuretics, n (%)	28 (93.3%)	32 (88.9%)
Thiazide diuretics, n (%)	3 (10.0%)	2 (5.6%)
Dihydropyridine calcium channel blockers, n (%)	2 (6.7%)	2 (5.6%)
Ivabradine, n (%)	5 (16.7%)	1 (2.8%)
Amiodarone, n (%)	1 (3.3%)	5 (13.9%)
Oral anticoagulants, n (%)	22 (73.3%)	29 (80.6%)

ACEI: Angiotensin-converting enzyme inhibitors; A2RB: Angiotensin II receptor blockers; ARNI: Dual angiotensin receptor and neprilysin inhibitor; HFpEF: Heart failure with preserved ejection fraction (left ventricular ejection fraction≥50%); NYHA: New York Heart Association.

Primary and secondary outcomes

The primary outcome, placebo-corrected change from baseline to week 16 in PVR, was not met since there was a median change of +0.09 WU (Q1-Q3, -0.49, +1.05 WU) in the mirabegron arm and a median change of -0.71 WU (Q1-Q3, -1.46, +0.84 WU) in the placebo arm (placebo-corrected difference in PVR of 0.62 WU (95%CI -0.38, 1.61; p=0.218). A similar result was obtained in the ITT population (placebo-corrected difference in PVR of 0.63 WU (95%CI -0.22, 1.51; p=0.152). **Table 3** shows the effect of mirabegron on the primary and pre-specified secondary outcomes. The study resulted positive for the pre-specified secondary outcome RV ejection fraction by advanced cardiac imaging (placebo-corrected change from baseline to week 16 of 3.0%, 95%CI= 0.4, 5.7%; p=0.026). No statistically significant differences were observed between both groups in the rest of pre-specified secondary outcomes.

Table 3: Effect of mirabegron on primary and secondary outcomes.

	Mirabegron (n=30)	Placebo (n=36)	Placebo-corrected mean difference (95%CI)	P value
Primary outcome				
PVR (WU)				
Baseline	4.00 (3.42-4.62)	4.66 (3.75-6.23)	0.62 (-0.38, 1.61)	0.218
Week 16	4.09 (3.00-5.88)	4.54 (2.23-6.14)		
Secondary outcomes				
RV ejection fraction (%)				
Baseline	44.9±10.1	45.5±9.3	3.0 (0.4, 5.7)	0.026
Week 16	48.3±8.8	45.0±9.6		
Mean PAP (mmHg)				
Baseline	40.2±9.6	44.0±10.1	-0.5 (-4.2, 3.3)	0.812
Week 16	38.3±10.6	40.9±8.2		
TPG (mmHg)				
Baseline	16.0 (14.0- 21.5)	19.0 (15.8, 28.0)	2.1 (-1.0, 5.2)	0.206
Week 16	15.6 (12.0-19.8)	18.0 (13.8-23.2)		
CO (L/min)				
Baseline	4.2±1.2	4.4±1.3	-0.2 (-0.6, 0.2)	0.391
Week 16	4.0±1.1	4.3±1.3		
Diastolic gradient (mmHg)				
Baseline	2.0 (0.0-5.8)	5.5 (1.8-8.2)	1.1 (-1.3, 3.3)	0.385
Week 16	3.0 (0.0-5.0)	3.0 (1.0-8.2)		
NYHA functional class				
Baseline II (n, %)	14 (46.7%)	21 (58.3%)		

III (n, %)	16 (53.3%)	15 (41.7%)	OR=0.34 (0.09-1.08)	0.077
Week 16 I (n, %) II (n, %) III (n, %)	 3 (10.0%) 15 (50.0%) 12 (40.0%)	 4 (11.1%) 24 (66.7%) 8 (22.2%)		
Quality of life (KCCQ overall summary score) (points)				
Baseline	58.8±21.3	64.9±18.9	-7.9 (-16.4, 0.6)	0.067
Week 16	60.3±20.2	70.6±20.7		
6-MWT distance (m)				
Baseline	357 (270-399)	368 (322-444)	5.3 (-25.1, 35.8)	0.720
Week 16	340 (281-414)	370 (314-434)		
Borg scale (points)				
Baseline	3.0 (1.0-5.0)	3.0 (1.2-4.0)	-0.4 (-1.7, 0.9)	0.581
Week 16	2.0 (1.0-4.0)	3.0 (1.2-4.8)		
NT-proBNP (pmol/L)				
Baseline	1391 (802-3106)	1750 (1140-2485)	-92 (-562, 364)	0.703
Week 16	1151 (741-2540)	1743 (1057-2645)		

Data are presented as mean±SD or median (1^{st}-3^{rd} quartile) as corresponding. CO: Cardiac output; KCCQ: Kansas City cardiomyopathy questionnaire; PAP: Pulmonary arterial pressure; PVR: Pulmonary vascular resistance; RV: Right ventricular; TPG: Transpulmonary gradient; 6-MWT: 6-minute walking test.

Prespecified subgroups analysis

Prespecified analysis of subgroups according to baseline left ventricular ejection fraction (<40% vs. ≥40%) and maximal tolerated dose were performed for the primary outcome. The interaction terms between dichotomized left ventricular ejection fraction (**Table 4**) and treatment or maximal tolerated dose (as an ordinal variable) and treatment were not significant (p values of 0.513 and 0.340, respectively). Similar results were obtained using the cut-off of 50% (data not shown). The effect of mirabegron after adjustment by left ventricular ejection fraction remained not statistically significant (0.52 WU; 95%CI -0.5, 1.54 WU) and neither after adjustment by maximal tolerated dose (0.62 WU, 95%CI -0.37, 1.6 WU). An exploratory (not prespecified) analysis did not show significant differences in treatment effect in patients in sinus rhythm or atrial fibrillation (data not shown).

Table 4: Pre-specified subgroup analysis.

	Mirabegron (n=30)		Placebo (n=36)		P value Interaction
	LVEF≥40 (n=21)	LVEF<40 (n=9)	LVEF≥40 (n=26)	LVEF<40 (n=10)	0.513
PVR					
Baseline	5.05 (2.46)	3.77 (0.90)	5.37 (2.36)	4.66 (1.83)	
Week 16	4.91 (3.09)	4.98 (3.14)	4.87 (1.99)	4.68 (3.37)	

PVR: Pulmonary vascular resistance; LVEF= Left ventricular ejection fraction.

Other variables

Supplemental Table 1 displays symptoms, physical examination and variables monitored during the 6-minute walking test, at baseline and 16-week follow-up. The percentage of patients presenting genitourinary symptoms or headache, typically associated with β3AR agonists, was very low. Mirabegron seemed not to affect heart rate, systolic blood pressure or oxygen saturation either at rest or after exercise.

Supplemental Table 1. Effect of mirabegron on symptoms, physical examination and parameters monitored during 6-minute walking test.

	Mirabegron (n=30)	Placebo (n=36)
Anamnesis		
Palpitations (n, %)		
Baseline	0 (0%)	2 (5.6%)
Week 16	2 (6.7%)	0 (0%)
Syncope (n, %)		
Baseline	0 (0%)	0 (0%)
Week 16	0 (0%)	0 (0%)
Chest pain (n, %)		
Baseline	1 (3.3%)	0 (0%)
Week 16	1 (3.3%)	0 (0%)
Orthopnea (n, %)		
Baseline	8 (26.7%)	4 (11.1%)
Week 16	5 (16.7%)	5 (13.9%)
Edemas (n, %)		
Baseline	5 (16.7%)	6 (16.7%)
Week 16	3 (10.0%)	8 (22.2%)
Geno-urinary symptoms (n, %)		
Baseline	1 (3.3%)	1 (2.8%)
Week 16	1 (3.3%)	0 (0%)
Headache (n, %)		
Baseline	2 (6.7%)	0 (0%)
Week 16	2 (6.7%)	0 (0%)

6-minute walking test		
Pre-test heart rate (bpm)		
Baseline	69.7±14.3	73.4±12.7
Week 16	71.7±13.5	69.4±12.8
Post-test heart rate (bpm)		
Baseline	87.7±22.1	93.1±18.4
Week 16	86.3±21.8	95.9±21.1
Pre-test systolic blood pressure (mmHg)		
Baseline	128.0±23.0	125.6±22.5
Week 16	131.1±21.9	121.9±24.1
Post-test systolic blood pressure (mmHg)		
Baseline	138.4±23.6	137.3±29.4
Week 16	139.0±22.4	131.4±27.7
Pre-test oxygen saturation (%)		
Baseline	96.6±1.6	95.7±3.3
Week 16	96.4±1.5	96.3±2.1
Post-test oxygen saturation (%)		
Baseline	91.8±6.9	92.3±6.6
Week 16	93.4±4.1	92.6±4.9

The effect of mirabegron on other (not included in the primary and secondary outcomes) systemic and pulmonary hemodynamics evaluated by right heart catheterization was neutral (**Supplemental Table 2**).

Supplemental Table 2: Effect of mirabegron on other hemodynamic variables on right heart catheterization.

	Mirabegron (n=30)	Placebo (n=36)
Heart rate (bpm)		
Baseline	65.3±9.5	70.1±11.8
Week 16	71.9±16.0	68.6±10.8
Oxygen saturation (%)		
Baseline	95.8±1.9	96.5±2.2
Week 16	96.2±1.7	96.5±1.6
Systolic blood pressure (mmHg)		
Baseline	138.2±26.1	134.8±22.3
Week 16	136.6±25.3	131.3±23.4
Systolic pulmonary arterial pressure (mmHg)		
Baseline	66.1±14.6	70.5±18.6
Week 16	63.3±18.6	65.8±15.7
Diastolic pulmonary arterial pressure (mmHg)		
Baseline	25.0±6.9	28.0±6.4
Week 16	23.9±8.1	26.9±6.9
Pulmonary capillary wedge pressure (mmHg)		
Baseline	21.7±5.1	22.4±4.6
Week 16	20.7±7.1	22.3±5.2
Right atrial pressure (mmHg)		

Baseline	11.0±4.6	12.0±5.4
Week 16	10.3±4.8	11.7±5.1
Right ventricular pressure (mmHg)		
Baseline	65.9±14.6	70.9±18.7
Week 16	64.4±18.3	65.6±15.8
Stroke volume index (ml/m^2)		
Baseline	35.2±9.3	34.7±8.4
Week 16	31.1±9.2	34.5±10.1
Cardiac index (L/min/m^2)		
Baseline	2.2±0.54	2.4±0.63
Week 16	2.2±0.47	2.3±0.63
Mixed oxygen saturation (%)		
Baseline	62.5±4.7	63.4±5.8
Week 16	60.5±7.8	62.9±7.4
Pulmonary arterial compliance (mL/mmHg)		
Baseline	1.6 (1.2-2.0)	1.5 (1.2-1.8)
Week 16	1.5 (0.9-2.0)	1.5 (1.2-2.0)

Supplemental Table 3 shows cardiac advanced imaging parameters not included in the primary or secondary outcomes and measures obtained by echocardiography. Globally, there were no robust differences in echocardiographic parameters between groups, except for a significant reduction in left atrial diameter (p=0.016) and a trend towards reduction of RV wall thickness (p=0.056) in the group of mirabegron. Regarding the association between imaging techniques, at baseline and 16-week evaluations, RV ejection fraction by CMR/CT significantly correlated with TAPSE, tricuspid S wave velocity, RV fractional area change and RV global longitudinal strain ($p<0.002$ for Pearson correlation in all cases). The highest correlation was found for RV fractional area change (R=0.75 at baseline and R=0.66 at follow-up, as previously observed[22]. Changes in RV ejection fraction by CMR/CT significantly correlated with changes in RV fractional area change (R=0.3, p=0.023).

Supplemental Table 3: Cardiac advanced imaging and echocardiography

Cardiac advanced imaging	Mirabegron (n=27)	Placebo (n=31)
Heart rate		
Baseline	65.6±14.5	67.9±12.6
Week 16	68.9±18.6	66.3±10.4
End-diastolic LV volume (ml)		
Baseline	184.9±108.4	198.3±110.0
Week 16	186.1±108.8	205.5±108.2
End-systolic LV volume (ml)		
Baseline	108.8±99.5	113.9±99.9

Week 16	108.5±103.3	116.7±99.6
LV ejection fraction (%)		
Baseline	49.5±17.1	49.4±16.2
Week 16	50.7±18.1	49.2±15.7
LV mass (g)		
Baseline	96.5±29.6	111.7±45.6
Week 16	98.7±36,4	116.8±47.9
End-diastolic RV volume (ml)		
Baseline	171.8±57.8	201.7±85.8
Week 16	179.5±58.9	207.1±89.1
End-systolic RV volume (ml)		
Baseline	94.5±42.1	113.5±60.9
Week 16	95.1±41.1	120.1±68.5
RV mass (g)		
Baseline	33.8±10.6	38.4±13.3
Week 16	34.0±9.2	35.4±14.5
Cardiac output (ml)		
Baseline	4.63 (3.94 -5.88)	5.04 (4.05-7.38)
Week 16	5.66 (4.75- 6.45)	5.58 (4.49-6.23)
Echocardiography	Mirabegron (n=30)	Placebo (n=36)
End-diastolic LV volume (ml)		
Baseline	140.7±113.6	159.7±113.5
Week 16	135.0±83.6	145.8±92.9
End-systolic LV volume (ml)		
Baseline	78.8±69.4	88.5±89.8
Week 16	75.9±69.7	80.4±73.9
LV ejection fraction (biplane) (%)		
Baseline	50.7±14.5	51.7±15.6
Week 16	52.8±15.2	52.0±16.7
RV fractional area change (%)		
Baseline	44.2±7.9	43.8±8.6
Week 16	45.7±7.2	44.1±9.0
RV wall thickness (mm)		
Baseline	6.7±2.2	6.9±2.0
Week 16	6.2±1.3	7.4±2.2
TAPSE (mm)		
Baseline	17.1±3.1	17.5±3.5
Week 16	16.7±2.8	17.6±3.1
Lateral mitral annular TD E’ wave (cm/s)		
Baseline	8.7±2.1	9.2±3.2
Week 16	8.9±2.8	8.3±2.4
Medial mitral annular TD E’ wave (cm/s)		
Baseline	6.0±2.0	6.0±2.0
Week 16	6.0±1.9	5.5±1.8
Lateral mitral E/E’		
Baseline	12.9±3.5	11.9±6.8
Week 16	12.8±4.6	12.8±6.9
Medial mitral E/E’		
Baseline	19.5±6.4	18.7±9.7
Week 16	19.5±8.4	21.9±10.8
TR severity (n, %)		

Baseline - Absent - Mild - Moderate - Severe	 1 (3.3%) 15 (50.0%) 11 (36.7%) 3 (10.0%)	 2 (5.6%) 17 (47.2%) 10 (37.8%) 7 (19.4%)
Week 16 - Absent - Mild - Moderate - Severe	 1 (3.3%) 16 (53.3%) 10 (33.3%) 3 (10.0%)	 2 (5.6%) 20 (55.6%) 6 (16.7%) 8 (22.2%)
Maximal TR jet velocity (cm/s)		
Baseline	350.5±51.6	360.9±53.1
Week 16	339.8±45.5	351.9±55.0
Cava vein diameter (mm)		
Baseline	19.1±4.2	19.9±5.9
Week 16	18.9±6.4	20.7±5.9
Pulmonary regurgitation (n, %)		
Baseline - Absent - Mild - Moderate - Not evaluable	 9 (30.0%) 15 (50.0%) 3 (10.0%) 3 (10.0%)	 20 (55.6%) 14 (38.9%) 1 (2.8%) 1 (2.8%)
Week 16 - Absent - Mild - Moderate - Not evaluable	 12 (40.0%) 13 (43.3%) 2 (6.7%) 3 (10.0%)	 17 (47.2%) 17 (47.2%) 1 (2.8%) 1 (2.8%)
Left atrial diameter (mm)		
Baseline	47.3±6.4	48.7±6.7
Week 16	45.8±5.9	49.5±5.6
TAPSE/PAPs (mm/mmHg)		
Baseline	0.29±0.1	0.30±0.1
Week 16	0.28±0.1	0.30±0.1
Tricuspid S wave (cm/s)		
Baseline	8.9±2.8	8.8±2.4
Week 16	9.0±2.6	8.9±2.4
RV myocardial performance index		
Baseline	0.6±0.2	0.6±0.2
Week 16	0.7±0.2	0.6±0.2
RV global longitudinal strain(%)		
Baseline	-17.6±5.2	-17.4±5.5
Week 16	-16.1±3.8	-16.8±6.0

LV: Left ventricular; RV: Right ventricular; TAPSE: Tricuspid annular plane systolic excursion; TD:

Tissue Doppler; TR: Tricuspid regurgitation.

Safety measures

A total of 238 adverse events (AEs) were reported, 119 in the mirabegron and 119 in the placebo group, regarding 74 patients (38 in the mirabegron and 36 in the placebo group) (**Table 5**). Severe AEs were reported in 11 patients in the mirabegron group and 9 in the placebo group. Of them, 6 events were considered to be related with the study medication by the independent data safety monitoring board, 3 in the mirabegron (chest pain in one patient, and incident atrial fibrillation and aggravated heart failure in another patient); and 3 in the placebo group (aggravated heart failure, incident atrial fibrillation and urinary tract infection). Study medication was discontinued because of serious AEs in 2 patients in the mirabegron group (HF decompensation and evidence of mitral rupture requiring surgery) and 2 patients in the placebo group (long QT in the context of sepsis, and a gastrointestinal bleeding). There were 2 deaths during the study, both in patients allocated to mirabegron. One patient presented a sudden cardiac death despite wearing an implantable automatic defibrillator. The second patient had been withdrawn from the study because of the presence of a mitral rupture requiring surgery and died in the postoperative period. None of them were considered to be related with the study drug. As shown in **Supplemental Table 4**, no clinically relevant changes were seen in vital signs, ECG or laboratory variables.

Table 5: Adverse events.

	Mirabegron (n=39)		Placebo (n=41)	
	Number of SAEs	Number of patients with AE (%)	Number of SAEs	Number of patients with AE (%)
Safety endpoint				
Death	2		0	
Hospitalization or need for iv furosemide due to heart failure	6	5 (13)	3	3 (7)
Investigator-reported adverse event				
Serious adverse events	17	11 (28)	14	9 (22)
SAE possibly related to the study drug	3	2 (5)	3	3 (7)
Any adverse event	119	38 (97)	119	36 (88)
Cardiac				
Heart failure, dyspnea or edemas	23	16 (41)	17	15 (37)

Incident or decompensated atrial or flutter fibrillation	3	3 (8)	3	3 (7)
Ventricular arrythmias	2	2 (5)	1	1 (2)
QT interval prolongation	2	2 (5)	4	4 (10)
Respiratory				
Respiratory tract infections	24	15 (38)	18	13 (32)
Urinary				
Urinary symptoms or infection	3	3 (8)	8	7 (17)
Nervous system				
Headache	4	3 (8)	2	2 (5)

Supplemental Table 4: Vital signs during physical examination, electrocardiogram and laboratory parameters.

	Mirabegron (n=39)	Placebo (n=41)
Physical examination:		
Body mass index		
Baseline	29.3±4.89	29.9±5.77
Week 16	29.4±4.32	29.0±5.58
Systolic blood pressure (mmHg)		
Baseline	126±19.6	123±20.5
Week 16	123±22.0	124±24.0
Heart rate (bpm)		
Baseline	70.4±12.8	72.6±14.9
Week 16	75.6±19.6	67.7±11.4
Oxygen saturation (%)		
Baseline	96.0±1.97	96.2±2.40
Week 16	96.3±1.62	96.4±1.56
ECG		
Heart rate (bpm)		
Baseline	69.5±14.3	71.7±14.7
Week 16	75.0±20.2	68.2±13.4
QT interval (mm)		
Baseline	417±42.2	431±42.1
Week 16	419±46.3	446±47.2
Corrected QT interval (mm)		
Baseline	413±28.8	426±23.1
Week 16	432±36.4	428±44.7
Blood parameters		
Glucose (mg/dl)		
Baseline	126±44.9	115±38.2
Week 16	123±38.6	123±46.0
Creatinine (mg/dl)		
Baseline	1.12±0.32	1.10±0.37
Week 16	1.12±0.32	1.15±0.35
Potassium (mg/dl)		
Baseline	4.30±0.50	4.41±0.64
Week 16	4.20±0.52	4.31±0.51
AST (UI/L)		
Baseline	24.3±7.59	28.9±12.9

Week 16	23.8±6.64	28.2±18.8
ALT (UI/L)		
Baseline	21.4±12.5	23.8±15.1
Week 16	23.1±11.3	21.8±15.3
Bilirubin (mg/dl)		
Baseline	0.81±0.46	1.05±0.74
Week 16	0.75±0.32	1.03±0.68
Hemoglobin (g/L)		
Baseline	12.7±1.80	12.8±1.88
Week 16	12.7±2.09	12.6±1.98

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Annex: Informed consent

HOJA DE INFORMACIÓN AL PACIENTE y CONSENTIMIENTO INFORMADO

Tratamiento con agonistas B3 en hipertensión pulmonar crónica secundaria a insuficiencia cardiaca (SPHERE-HF)

INTRODUCCIÓN

Usted ha sido atendido en la Unidad de Insuficiencia Cardíaca del Hospital Clínic de Barcelona por presentar una enfermedad del corazón (patología cardíaca izquierda) evolucionada, que le está causando cada vez más cansancio y dificultad para respirar.

Se ha confirmado por parte del equipo médico que usted está tomando la medicación adecuada para esta enfermedad y a las dosis máximas toleradas. La evolución natural de una patología cardíaca izquierda avanzada, es la aparición de hipertensión pulmonar y posteriormente disfunción de la cavidad ventricular derecha, lo que comporta el estadio final de la enfermedad, sin que en la actualidad dispongamos de opciones terapéuticas.

En estudios con animales experimentales hemos observado que el tratamiento con fármacos que actúan sobre los receptores B3 adrenérgicos (proteínas presentes en su corazón y vasos sanguíneos), reduce la hipertensión pulmonar y mejora la función del corazón. Este tratamiento (mirabegron) está actualmente comercializado para personas con otro problema médico (vejiga hiperactiva) y el fármaco tiene un buen perfil de seguridad.

Necesitamos estudios que nos permitan evaluar la eficacia y seguridad de este tratamiento en pacientes con insuficiencia cardiaca e hipertensión pulmonar, y así evaluar la mejora clínica y el pronóstico de pacientes como usted.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico, ni se produzca perjuicio alguno en su tratamiento.

OBJETIVOS DEL ESTUDIO

Este estudio pretende evaluar la eficacia y seguridad del tratamiento con mirabegron en pacientes, con hipertensión pulmonar secundaria a cardiopatía izquierda.

METODOLOGÍA

Inicialmente, realizaremos una **entrevista clínica completa** para conocer mejor sus antecedentes. Posteriormente, se realizarán una serie de exploraciones:

Analítica sanguínea: extracción de una muestra de sangre para analizar parámetros de rutina relacionados con la insuficiencia cardiaca. Asimismo, en aquellos pacientes que den su consentimiento informado específico se extraerá una muestra extra de sangre que se centrifugará para obtener suero o plasma y congelarlo a fin de poder analizar los mecanismos involucrados en la aparición de Hipertensión Pulmonar secundaria a insuficiencia cardíaca y los mecanismos de acción del mirabegron. Estas muestras se guardarán en las serotecas ubicadas en el Hospital Clínic, Hospital de Sant Pau y CNIC. Este plasma congelado sólo podrá utilizarse, en caso que Usted dé permiso para ello y dicha autorización es independiente de su voluntad de participar en el estudio, y para los objetivos citados en el presente protocolo.

Electrocardiograma (representación gráfica de la actividad eléctrica del corazón)

Test de la marcha de 6 minutos: deberá caminar por un pasillo, entre los puntos indicados por unos conos, tal y como le explicará la enfermera. También se le tomará la presión arterial y la saturación de oxígeno (prueba muy utilizada para conocer el contenido de oxígeno en sangre y que consiste en colocar un pequeño aparato tipo pinza en un dedo de la mano)

Ecocardiografía: prueba no invasiva (ultrasonidos) que permite ver imágenes del corazón en movimiento, con estudio detallado de la cavidad ventricular derecha

Resonancia Magnética Cardíaca: consiste en la adquisición de imágenes de su corazón mediante una máquina de utiliza campos magnéticos, que permite obtener información de muy alta calidad, para estudiar la función del ventrículo derecho y la arteria pulmonar. En caso de existir una contraindicación para la realización de la resonancia magnética cardiaca (dispositivos metálicos tipo marcapasos o desfibriladores no compatibles o claustrofobia grave) se le ofrece la opción de realizar una **tomografía computarizada cardiaca**. Está técnica consiste en la adquisición de imágenes de su corazón en movimiento mediante rayos X.

Cateterismo derecho: consiste en la medición de la presión en su arteria pulmonar. Se trata de colocar un catéter, en una vena (yugular o femoral según el caso) y hacer que llegue a través de la vena cava, la aurícula y el ventrículo derecho hasta la arteria pulmonar. De esta forma podremos medir con certeza dicha presión (la ecografía nos da solamente una aproximación que no siempre se corresponde con la realidad) y medir su gasto cardíaco (volumen de sangre que su ventrículo es capaz de bombear a lo largo de un minuto). Ésta prueba puede conllevar complicaciones, aunque de forma muy infrecuente. Algunas de ellas son: hematoma en la zona de punción, neumotórax, infección, hemorragia pulmonar, arritmias ventriculares. Pese a ello, sabemos que conocer los datos derivados de esta exploración es importante para evaluar el efecto del tratamiento administrado.

Estas pruebas se realizarán **en el momento de inclusión en el estudio y de nuevo tras aproximadamente 4 meses** de tratamiento, para poder evaluar el efecto del fármaco en el grado de hipertensión pulmonar y en la función de su ventrículo derecho.

Cuando comience el tratamiento, tomará una dosis pequeña del fármaco en estudio (mirabegron o placebo) que se irá aumentando cada 2 semanas, según su respuesta clínica y lo observado en el electrocardiograma.

Durante todo el estudio se realizarán un total de 9 visitas de seguimiento: la inicial, a la semana del inicio del tratamiento, a las 2 - 4 - 6 - 8 - 12 y 16 semanas, y finalmente una última visita, alrededor de los 30 días de finalizar la medicación del estudio.

CONFIDENCIALIDAD

Su participación en el estudio es totalmente confidencial. Sus derechos, en cuanto a sus datos personales se refiere (nombre y apellidos, nº de historia clínica, dirección etc.), no se verán afectados de ninguna manera, ya que este estudio se llevará a cabo de acuerdo a la Ley Orgánica de Protección de datos de Carácter Personal 15/1999, de 13 de diciembre.

De acuerdo a lo que establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio.

De conformidad con la normativa vigente en materia de protección de datos, usted consiente que sus datos médicos requeridos por el estudio, se manden debidamente codificados/enmascarados al promotor del mismo.

El acceso a su información personal quedará restringido al médico del estudio o colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen, para comprobar

datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.

Sólo se recogerá la información necesaria para cumplir con los objetivos científicos del estudio.

BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO y TRATAMIENTOS ALTERNATIVOS

Tendrá la oportunidad de beneficiarse de probar un tratamiento potencialmente beneficioso, para una enfermedad para la que no disponemos de tratamiento específico aprobado.

No se le puede asegurar que obtenga algún beneficio de su participación en este estudio. Sin embargo, la información obtenida durante el transcurso del mismo puede ayudarnos a comprender mejor la enfermedad en general, y la suya en particular. También puede ayudarnos a seleccionar el tratamiento más adecuado que prolongue su supervivencia y calidad de vida, así como la de otros pacientes que presentan su misma patología.

SEGURO

El Promotor del estudio ha contratado una póliza de seguros con una compañía que se ajusta a la legislación vigente y que cubre todos los posibles daños y lesiones que pudieran producirse en relación con su participación en el estudio.

COMPENSACIÓN ECONÓMICA

Su participación en este estudio no le supondrá ningún gasto, pero tampoco recibirá ninguna compensación por su participación en el mismo.

De existir algún gasto extraordinario (desplazamiento a visitas del estudio…) éste le sería reembolsado.

ASPECTOS ÉTICOS

El Comité Ético de Investigación Clínica designado, aprobó este proyecto de investigación, así como esta hoja de información y consentimiento, según regulación aplicable a este tipo de estudios.

Además, deberá aprobar cualquier revisión o modificación del protocolo de investigación, de la hoja de consentimiento informado o de la hoja de información al paciente.

El presente estudio se llevará a cabo de acuerdo a lo establecido en el RD 1090/2015 de 4 de diciembre, que regula los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos; Real Decreto Legislativo 1/2015, de 24 julio Ley de garantías y uso racional de medicamentos y productos sanitarios; Real Decreto 577/2013 de 26 de julio, que regula la fármaco-vigilancia, y la Ley 14/2007 de 3 de julio de Investigación Biomédica, todas ellas en lo que les sea de aplicación, así como la Declaración de Helsinki y las guías de buena práctica clínica y recomendaciones de la ICH

PREGUNTAS

Si tiene alguna pregunta sobre el estudio, le rogamos se comunique con el investigador responsable o el personal implicado en el estudio:

Investigador Principal: Dra Ana García Álvarez

Teléfono: 93 227 54 00 Extensión 2912

CONSENTIMIENTO por ESCRITO del PACIENTE

Tratamiento con agonistas B3 en hipertensión pulmonar crónica secundaria a insuficiencia cardiaca (SPHERE-HF)

Yo (nombre y apellidos) ……...

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido respuestas satisfactorias a mis preguntas.

He recibido suficiente información sobre el estudio.

He hablado con el Dr: .....

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1º Cuando quiera

2º Sin tener que dar explicaciones

3º Sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

_____	_____
Fecha (paciente)	**Firma del paciente**
_____	_____
Fecha (investigador)	**Firma del investigador**

Sin que su decisión en este apartado afecte su voluntad de participar en este ensayo clínico, accede a que las muestras de sangre obtenidas durante el estudio, puedan ser utilizadas en el futuro para nuevos análisis relacionados con la enfermedad o fármacos del estudio no previstos en el protocolo actual (quedando excluidos los análisis genéticos, siempre y cuando no formen parte de los objetivos del estudio)

SI □ NO □

_____	_____
Firma del paciente	**Firma del investigador**

1 ejemplar para el paciente, 1 ejemplar para el investigador

CONSENTIMIENTO por ESCRITO del REPRESENTANTE

Tratamiento con agonistas B3 en hipertensión pulmonar crónica secundaria a insuficiencia cardiaca (SPHERE-HF)

Yo (nombre y apellidos)……..

en calidad de (relación con el participante) …….

de (nombre y apellidos del participante) …….

He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido respuestas satisfactorias a mis preguntas.
He recibido suficiente información sobre el estudio.

He hablado con el Dr: .....

Comprendo que la participación del paciente es voluntaria.
Comprendo que puede retirarse del estudio:
1º Cuando quiera
2º Sin tener que dar explicaciones.
3º Sin que esto repercuta en sus cuidados médicos.

Y presto mi conformidad para que (nombre del participante) …… participe en este estudio y doy mi consentimiento para el acceso y utilización de los datos en las condiciones detalladas en la hoja de información.

_____ _____
Fecha (representante) **Firma del representante**

_____ _____
Fecha (investigador) **Firma del investigador**

Sin que su decisión en este apartado afecte su voluntad de participar en este ensayo clínico, accede a que las muestras de sangre obtenidas durante el estudio, puedan ser utilizadas en el futuro para nuevos análisis relacionados con la enfermedad o fármacos del estudio no previstos en el protocolo actual (quedando excluidos los análisis genéticos, siempre y cuando no formen parte de los objetivos del estudio)

SI □ NO □

_____ _____
Firma del paciente **Firma del investigador**

1 ejemplar para el paciente, 1 ejemplar para el investigador

Barcelona 25/05/2018

Apreciado Participante,

A partir del 25 de mayo de 2018 es de plena aplicación la nueva legislación en la UE sobre datos personales, en concreto el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD). Por ello, es importante que conozca la siguiente información:

- Además de los derechos que ya conoce (acceso, modificación, oposición y cancelación de datos) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio. Le recordamos que los datos no se pueden eliminar aunque deje de participar en el ensayo para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.
- Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).
- El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.
- Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar con el Delegado de Protección de Datos del promotor [*protecciodades.recerca@clinic.cat*].

Saludos cordiales,

Firmado:

_____

Dra. Ana García Álvarez
Investigadora Principal
Hospital Clínic de Barcelona