Clinical trial results:
3 adrenergic agoniSt treatment in chronic Pulmonary HypERtEnsion secondary to heart failure: a randomized placebo-controlled phase 2 clinical trial

Summary

EudraCT number	2016-002949-32
Trial protocol	ES
Global end of trial date	04 June 2021

Results information

Result version number	v1 (current)
This version publication date	29 December 2022
First version publication date	29 December 2022
Summary attachment (see zip file)	Sphere_End of Study EMA (SPHERE_ End of study EMA.pdf)

Trial information

Trial identification

Sponsor protocol code	SPHERE-HF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02775539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundació Clínic per la Recerca Biomédica
Sponsor organisation address	c/ Villarroel, 170, Barcelona, Spain, 08036
Public contact	Dra. Ana García Álvarez, Fundació Clínic per la Recerca Biomédica, 34 9322754004031, ANAGARCI@clinic.cat
Scientific contact	Dra. Ana García Álvarez, Fundació Clínic per la Recerca Biomédica, 34 9322754004031, ANAGARCI@clinic.cat
Sponsor organisation name	CNIC
Sponsor organisation address	c/ Melchor Fernández Almagro 3, Madrid, Spain, 28029
Public contact	Ana Gracía Álvarez, CNIC, 34 9145312001507, ana.garcia@cnic.es
Scientific contact	Ana Gracía Álvarez, CNIC, 34 9145312001507, ana.garcia@cnic.es

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2021
Global end of trial reached?	Yes
Global end of trial date	04 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective is to evaluate the efficacy and safety of mirabegron for the treatment of patients with PH secondary to HF. The primary objective is changes in PVR after 16 weeks of treatment.

Protection of trial subjects:

Due to the characteristics of the study has not been used specific measurements.

Background therapy: -

Evidence for comparator:

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

Actual start date of recruitment	09 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	28
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Spain at five sites of Barcelona and Madrid, and was start on 21 June 2017 with the first patient enrolled. The recruitment was for 2 years with a follow-up of 5 months. The last patient completed (end of study) was on 4 June 2021.

Pre-assignment

Screening details:

Patients with PH associated with HF were screened. 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.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

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.

Arms

Are arms mutually exclusive?	No
Arm title	Mirabregon

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Mirabegron
Investigational medicinal product code	YM178
Other name	Betmiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Mirabegron: 50 mg daily, titrated till 200 mg daily for 16 weeks.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo: 50 mg daily, titrated till 200 mg daily, for 16 weeks. 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.

Number of subjects in period 1	Mirabregon	Placebo
Started	39	41
NA	37	41
Completed	37	41
Not completed	2	0
Adverse event, serious fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Mirabregon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Mirabregon	Placebo	Total
Number of subjects	39	41	80
Age categorical Units: Subjects			
Adults (18-64 years)	11	17	28
From 65-84 years	28	24	52
Gender categorical Units: Subjects			
Female	24	23	47
Male	15	18	33

Subject analysis sets	
Subject analysis set title	Final analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Of the 151 patients screened from June 2017 to December 2020, 81 were initially considered eligible for randomization. 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 was ineligible for the study.

Reporting group values	Final analysis		
Number of subjects	80		
Age categorical Units: Subjects			
Adults (18-64 years)	28		
From 65-84 years	52		
Gender categorical Units: Subjects			
Female	47		
Male	33		

End points

End points reporting groups

Reporting group title	Mirabregon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Final analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Of the 151 patients screened from June 2017 to December 2020, 81 were initially considered eligible for randomization. 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 was ineligible for the study.

Primary: PVR by RHC

End point title	PVR by RHC

End point description:

Primary outcome will be the change from baseline to week 16 in PVR by RHC. PVR will be calculated in Wood units as: (mean PAP [in mmHg] – PAWP [in mmHg])/cardiac output (L/min).

End point type	Primary

End point timeframe:

After 16 weeks of treatment.

End point values	Mirabregon	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: wood	39	41		

Statistical analyses

Statistical analysis title	Statistical and analytical plans
Comparison groups	Mirabregon v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	> 0.1
Method	ANCOVA

Notes:

[1] - 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).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 20 september 2017 to 10 March 2021

Adverse event reporting additional description:

Were reported a total of 238 adverse events (AEs).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Mirabegron

Reporting group description: -

Serious adverse events	Placebo	Mirabegron	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 41 (21.95%)	11 / 39 (28.21%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Heart failure, dyspnea or edemas			
subjects affected / exposed	9 / 41 (21.95%)	11 / 39 (28.21%)	
occurrences causally related to treatment / all	3 / 14	3 / 17	
deaths causally related to treatment / all	0 / 0	0 / 2	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Mirabegron	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 41 (87.80%)	38 / 39 (97.44%)	
General disorders and administration site conditions			
other			
alternative assessment type: Non-systematic			
subjects affected / exposed	36 / 41 (87.80%)	38 / 39 (97.44%)	
occurrences (all)	119	119	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2018	The initial version of the SPHERE-HF clinical trial included as exclusion criteria: "Corrected QT interval in ECG >430 ms in men or >450 ms in women", which are the values described of corrected QT interval in the healthy population in some registries (although it is more common to use the values of 450 ms in males and 460 ms in women, as established in clinical practice guidelines [Rautaharju. JACC 2009]). However, we have found that these criteria exclude a very high percentage of patients with heart failure who could potentially a very high percentage of patients with heart failure who could potentially benefit from this therapy, since it is known that in the presence of heart disease the QT interval is prolonged and also shows greater circadian variation (P.P. Davey, Br Heart J 1994; P Davey, Eur Heart J 2000; Davey PP Clin Sci 2000). In summary, considering that: 1. Mirabegron does not significantly prolong the QT interval. 2. The SPHERE-HF clinical trial is specifically designed to evaluate the safety of mirabegron treatment in pulmonary hypertension secondary to heart failure, so that you start with the 50 mg dose of mirabegron (dose used for overactive bladder) and an electrocardiogram is mandatory before starting each dose. 3. The current QTc criterion excludes a very high percentage of the target population: patients with heart failure. We request to modify the exclusion criterion to: "Corrected QT interval on ECG >480 ms", which coincides with the definition of pathological prolongation of the QT interval. In addition, the same value shall be included in the recommended titration protocol, such that QTc interval >480 ms should be reduced or discontinued, but not titrated upwards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported