ß3-adrenergic receptor agonists for the treatment of chronic pulmonary hypertension

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On behalf of Dr. Ana García-Álvarez, MD, PhD, PI of the SPHERE-HF Project.

Madrid, 29 de octubre de 2019

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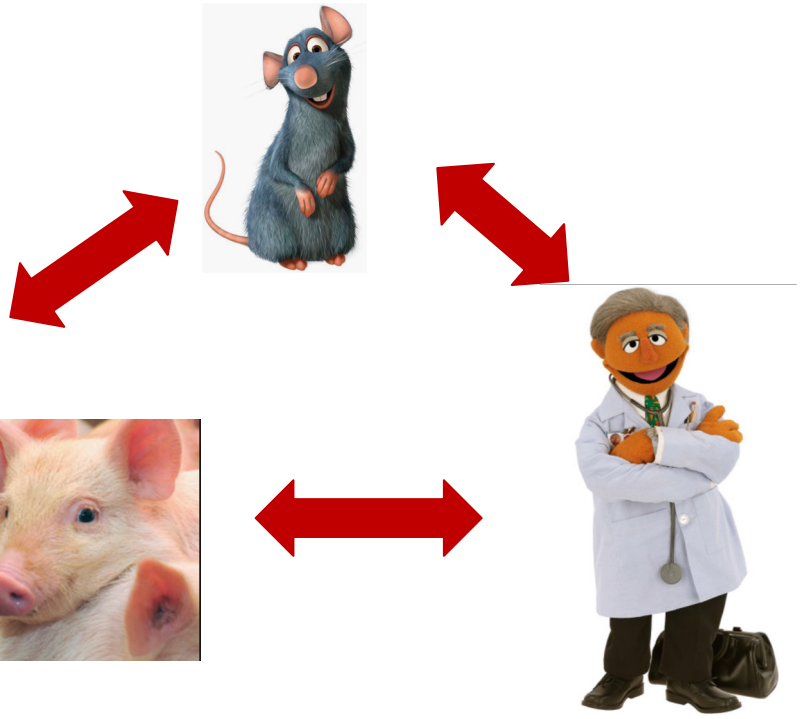
The Institutions

- The Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is a **leading international research center** dedicated to understanding the basis of cardiovascular health and disease and to translating this knowledge into improved patient care.



TRANSLATIONAL RESEARCH

The Institutions

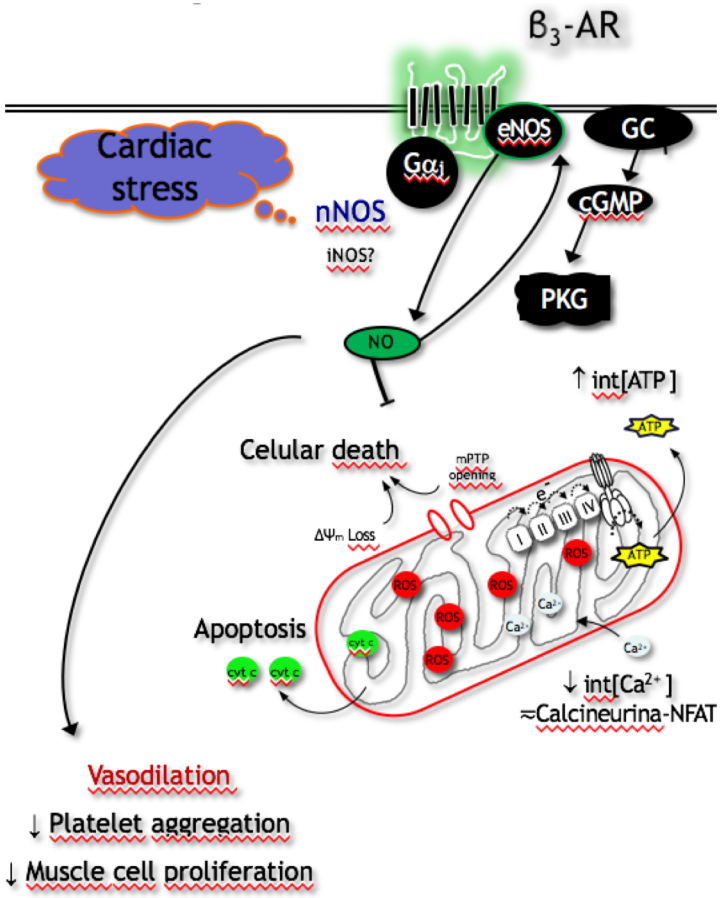
FUNDACIÓ CLÍNIC BARCELONA

- The Clinic Foundation's mission is to offer a portfolio of excellent services to the research and innovation communities that consolidate the organization as a national and international referent. The goal is to contribute to **improving the health and quality of life of the population** level through **the competence, the skills, a responsible sustainable work and a scientific and social orientation.**

The product: Target indications

- The present proposal claims the use of **β3-adrenergic receptor agonists (β3AR agonists)** for the treatment of **chronic pulmonary hypertension.**
- β3AR agonists, particularly Mirabegron (Betmiga®), are currently used for the treatment of hyperactive bladder syndrome.
- There are two major classes of β3AR agonists, the phenylethanolamines (comprising BRL37344, SR58611A, and CL316243) and aryloxypropanolamines (including mirabegron, cyanopindolol and CGP12177A). Distinctive pharmacodynamic properties of β3AR, such as their **upregulation in disease** and **resistance to desensitization**, suggest that they may be attractive targets for therapeutic intervention.

The product: Innovative mechanisms of action

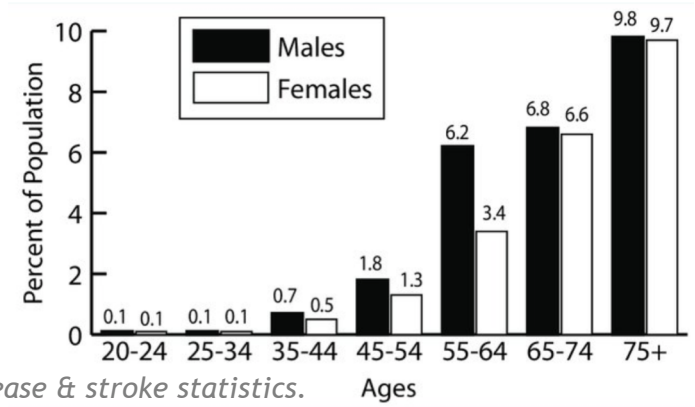


- B3AR mRNA expression has been found in the human myocardium and vessels[1] and is **upregulated in cardiovascular disease**[2].
- B3ARs are coupled to **G proteins** and their downstream pathway includes nitric oxide synthase (NOS), NO-activated guanylyl cyclase and **cGMP synthesis**, and increased **cAMP synthesis**[3].
- Loss of cGMP and cAMP signaling is a hallmark in PH[4,5].
- **Cyclic nucleotides** are responsible for mediating endothelin-dependent **dilatation** and also have salutary actions on pulmonary vascular remodeling, fibrosis, and right ventricular (RV) function[6,7].

1. Rozec B. Pharmacol Ther 2006.
2. Moniotte S. Circulation 2001.
3. Gauthier C. J Clin Invest 1998.
4. Humbert M. JACC 2004.
5. Moraes DL. Circulation
6. Dumas M. Eur J Pharmacol 1998.
7. Tagaya E. Lung 1999.

The product: Differential features facing the market

- Pulmonary hypertension is a **substantial global health issue.**
- Present estimates suggest a **PH prevalence** of about **1%** of the global population worldwide, which increases up to **10% in individuals aged 65 or more[1].**
- The most frequent cause of PH is **heart failure** (group II PH in the current classification) followed by lung disease (group III PH)[2].
- Heart failure is a rapidly growing public health issue with an estimated prevalence of **>37.7 million individuals** globally[3]. This number is expected to rise in the upcoming years due to the global ageing of the population. Thus, PH incidence will also increase.
- Few therapies with **high cost** and **limited beneficial effect** are currently available for PAH (group I)[2,4].



Data from AHA heart disease & stroke statistics.

1. Hoeper. Lancet Respir Med 2016.
2. Galie. ESC guidelines on PH. EHJ 2016.
3. Ziaeian. Nature Reviews Cardiology 2016.
4. Vachiery. European Resp J 2019.

Recommendations	Class[a]	Level[b]
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease)	I	B
It is recommended to identify other causes of PH (i.e. COPD, sleep apnoea syndrome, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD	I	C
It is recommended to perform invasive assessment of PH in patients on optimized volume status	I	C
Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic workup and an individual treatment decision	IIa	C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation	III	C
The use of PAH-approved therapies is not recommended in PH-LHD	III	C

Treatment for groups 2 and 3 PH

The product: Differential features facing the market

- If proven beneficial, β3AR agonists would be the **first chronic pharmacological treatment** for PH due to left heart disease (and eventually also for pulmonary disease).

- β3AR agonists have demonstrated an **additional cardioprotective effect** (prevention of left ventricular fibrosis and remodeling) in experimental studies using animal models of heart failure[1,2].

- Distinctive pharmacodynamic properties of β3AR, such as their **upregulation in disease** and **resistance to desensitization**, suggest that they may be attractive targets for therapeutic intervention.

- Mirabegron (Betmiga®), is an oral β3AR agonist used for other condition (overactive bladder syndrome) with a **good safety profile.**

1.Niu X. JACC 2012.
2. Belge C. Circulation 2014.

The product: Current status of development

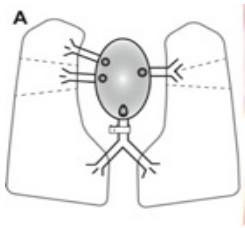
Own translational research in PH.

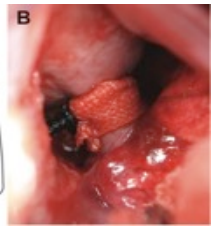
Hypothesis: β3AR stimulation may be a potential target in PH acting through vasodilatation (and maybe vascular remodeling inhibition) and prevention of RV dysfunction.

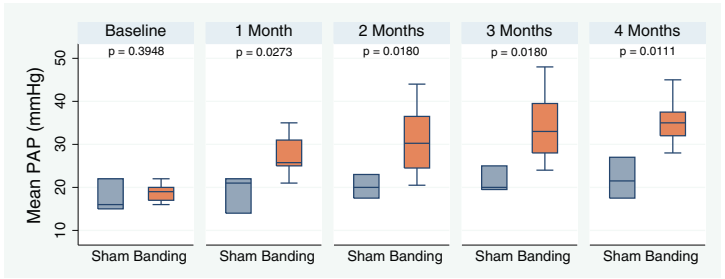
Effect in acute PH

Acute pulmonary embolization
- Microspheres
- Multiple doses from a suspension 2.5 mg/ml
- PAPm≥40 mmHg

Effect in chronic PH



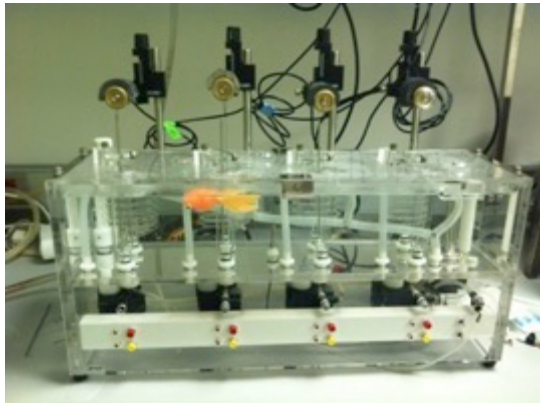




P27
Ki67

Human samples

Real-time PCR

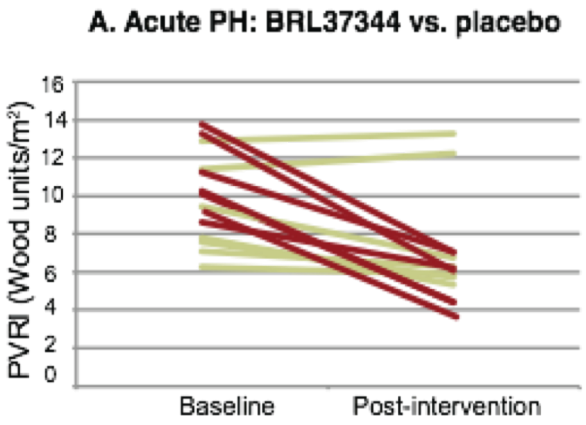


Organ bath studies

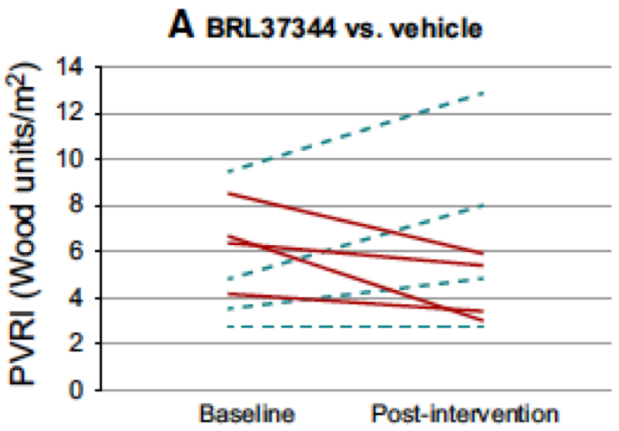
D Pereda et al. JCV Trasl. Med 2014

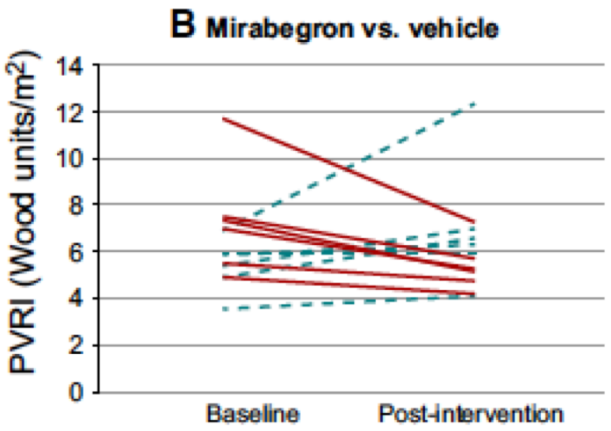
The product: Current status of development

HD effect in acute PH



HD effect in chronic PH





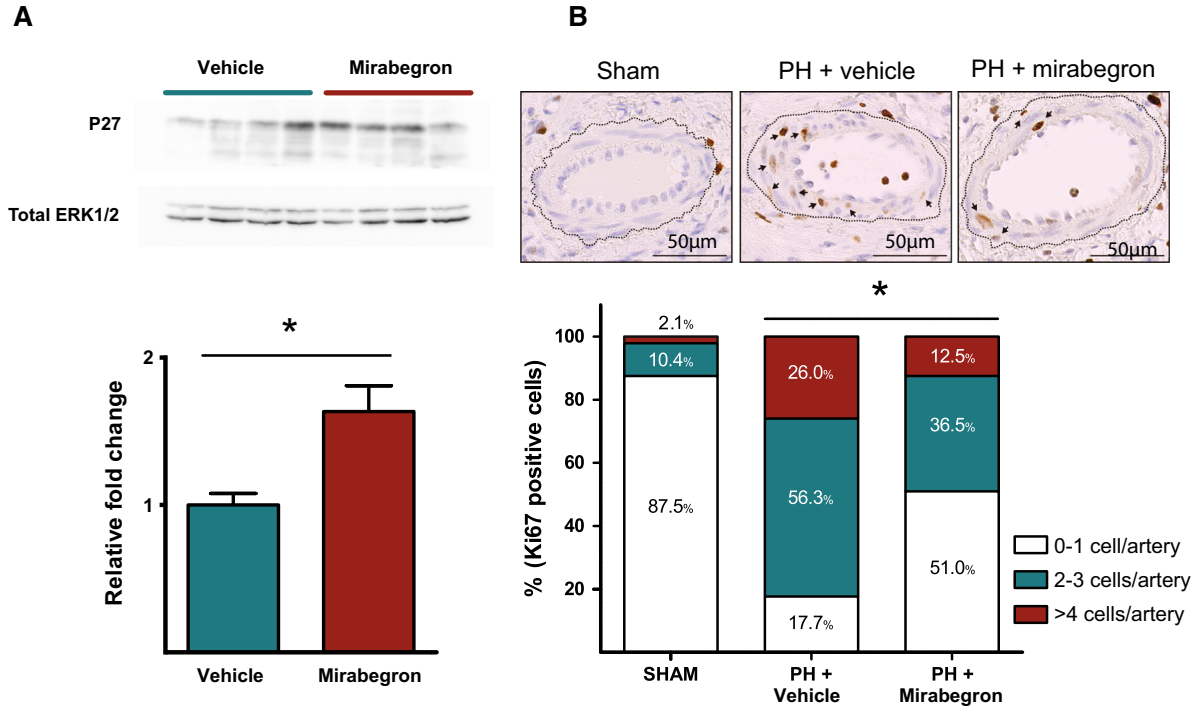
"B3AR stimulation significantly reduces PVR and improves RV performance in a translational model of chronic PH".

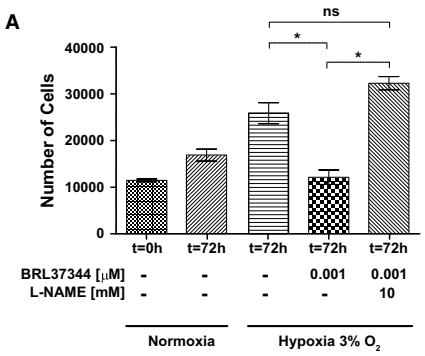
RV end-diastolic volume index (ml/m^2)	99.3 (20.6)	104.0 (15.5)	101.4 (16.5)	92.2 (16.8)	3.6 (18.2)	−4.0 (26.1)	0.143
RV end-systolic volume index (ml/m^2)	37.9 (18.4)	46.6 (16.1)	43.7 (5.3)	39.7 (7.0)	6.5 (15.7)	−5.4 (9.8)	**0.009**
LV end-diastolic volume index (ml/m^2)	97.1 (9.5)	90.3 (17.7)	93.2 (11.8)	93.3 (17.3)	−1.4 (16.4)	3.4 (11.3)	0.436
LV end-systolic volume index (ml/m^2)	35.5 (11.0)	36.2 (9.0)	37.5 (8.7)	37.2 (11.6)	1.0 (7.7)	1.0 (7.7)	0.971
RV mass index (g/m^2)	28.1 (8.1)	26.6 (7.6)	28.1 (8.2)	27.6 (3.6)	0.0 (8.3)	1.9 (8.3)	0.796
LV mass index (g/m^2)	58.8 (11.4)	52.6 (9.1)	62.1 (7.0)	60.1 (8.3)	−2.1 (17.6)	7.3 (15.8)	0.247
RV ejection fraction (%)	61.9 (13.0)	52.0 (6.4)	56.4 (5.6)	58.4 (7.8)	−3.6 (9.3)	5.0 (5.2)	**0.007**
LV ejection fraction (%)	63.5 (4.2)	59.8 (6.1)	61.9 (6.3)	61.2 (6.39	−1.0 (4.6)	0.6 (6.3)	0.280
PA average velocity (m/s)	11.0 (3.3)	10.5 (4.9)	11.7 (3.7)	12.3 (3.2)	0.9 (2.7)	1.9 (2.5)	**0.019**

A García-Álvarez, D Pereda et al. Basic Res Cardiol 2016.

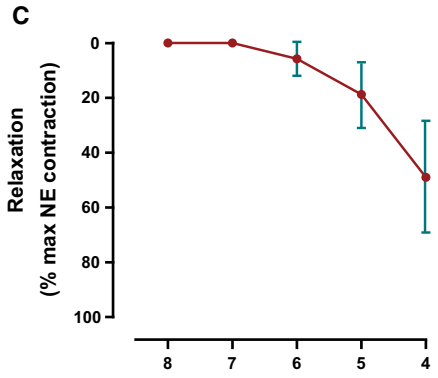
The product: Current status of development

Pulmonary vascular remodeling & human arteries studies





"B3AR stimulation reduces proliferation of human PA SMCs in a NO-dependent manner".



"B3AR stimulation produces a change in protein expression associated with a decrease in vascular cell proliferation in the pulmonary parenchyma".

"B3AR stimulation produces vasodilation of human pulmonary arteries ex-vivo".

A García-Álvarez, D Pereda et al. Basic Res Cardiol 2016.

The product: Current status of development

Own research in PH: Pilot clinical trial

La Marató 3

B3 adrenergic agoniSt Treatment in Chronic Pulmonary HypERtEnsion Secondary to Heart Failure: a Randomized Placebo-Controlled Phase 2 Clinical Trial

SPHERE-Heart failure trial

Aim

To evaluate the efficacy and safety of Mirabegron in patients with PH secondary to heart failure.

PI: Dr. Ana García-Álvarez (H. Clínic/CNIC).

The product: Current status of development

SPHERE-HF trial design

Random allocation to mirabegron or placebo

First study medication dose

Last study medication dose

Sphere-HF is a **phase-2 multicenter randomized placebo-controlled clinical trial** that will enroll 80 patients with combined **pre- and post-capillary pulmonary hypertension secondary to HF**. Patients are randomized 1:1 to the **β3AR agonist mirabegron** (uptitrated until 200 mg/day) or placebo.

Screening phase

Evaluation inclusion/exclusion criteria & baseline studies.

V0 V1 V2 V3 V4 V5 V6 V7 V8 V9

30 days

Dose adjustment phase

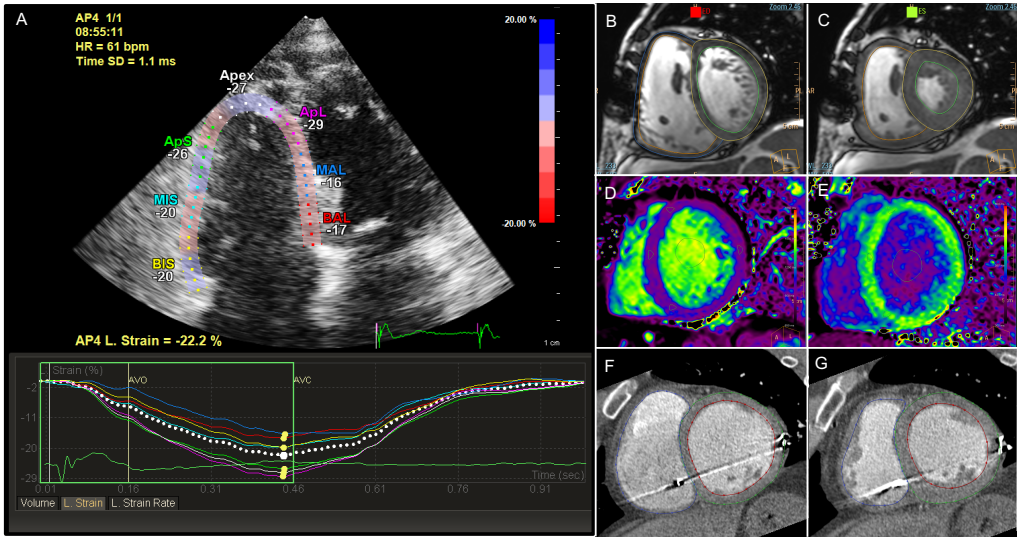
Maintenance phase

8 weeks

8 weeks

The primary efficacy outcome is the change in **PVR** from baseline to week 16, assessed by right heart catheterization.

Secondary efficacy outcomes include **clinical, biochemical** and **hemodynamic** parameters as well as **functional status** and **RV function** evaluated with multimodality cardiac imaging (echocardiography and cardiac magnetic resonance/cardiac computed tomography).



The product: Current status of development

SPHERE-HF trial design

	V0-V1	V2	V3	V4	V5	V6	V7	V8	V9
Informed consent	x								
Inclusion/exclusion criteria	x								
Demographic & clinical variables	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/CCT	x							x	

The product: Current status of development

SPHERE-HF current recruitment status

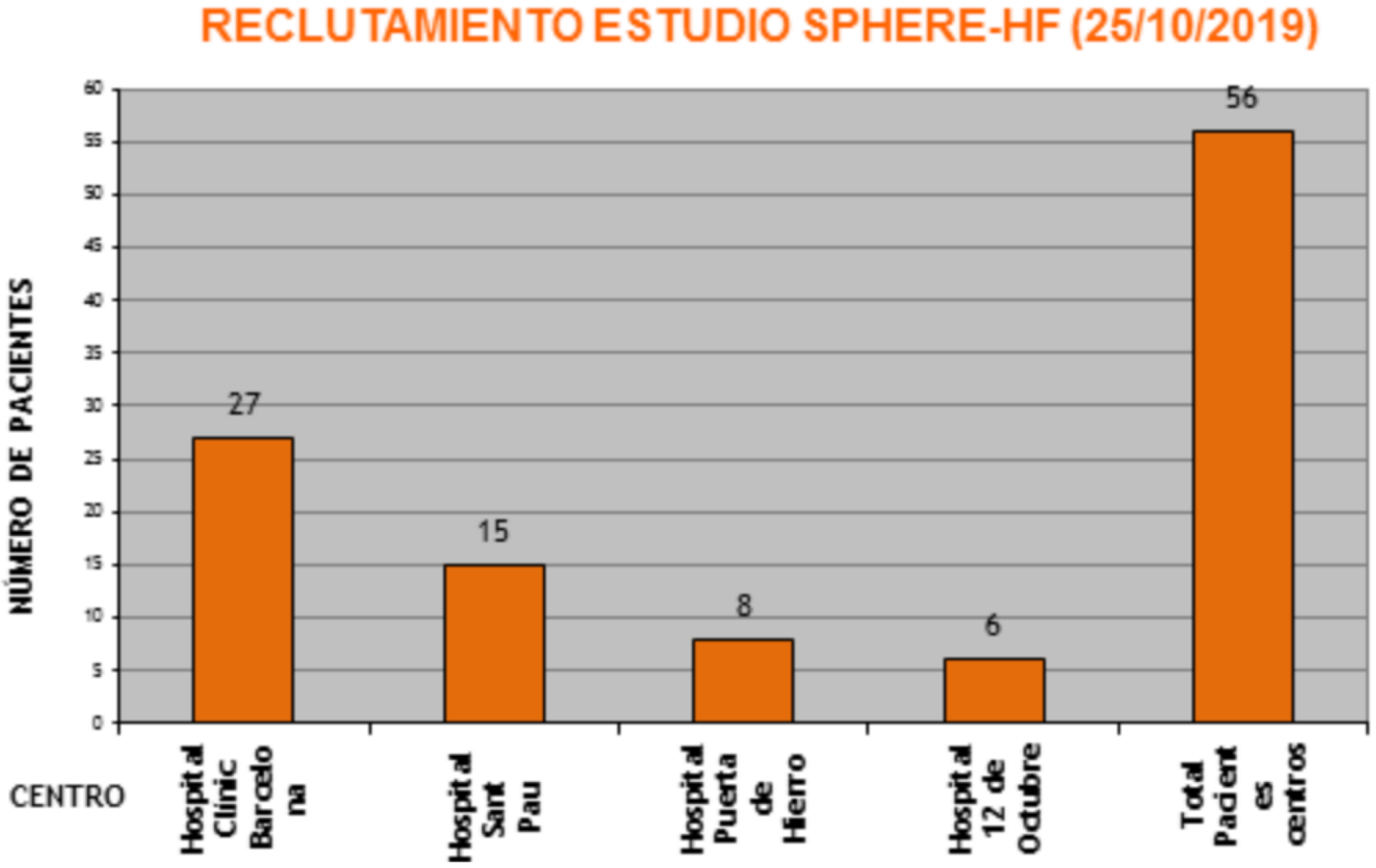
	Randomized patients	Patients on follow-up	End of follow-up	Incomplete follow-up	% respect prevision
Hospital Clínic	27	3	19	5	96%
Hospital Sant Pau	15	1	14	1	62%
Puerta de Hierro	8	3	4	1	57%
12 de Octubre	6	0	6	0	42%
Total	56	6	43	7	70%

6/2017: H. Clinic opening.
10/2017: H. Sant Pau/HUPH / H120 opening.
12/2019: Estimated end of recruitment.

CLÍNIC BARCELONA Hospital Universitari

The product: Current status of development

SPHERE-HF current recruitment status



The product: IPR protection

- CNIC and Fundació Clinic per la Recerca Biomèdica (Dr. Borja Ibáñez, Dr. Ana García-Álvarez, Dr. Valentín Fuster), as co-owners of this invention filled in a related European patent application on August 29th, 2012 entitled **"Beta-3 adrenoceptor agonists for the treatment of pulmonary hypertension"**.

- In 2015 this patent application entered into national phases in Europe (pending), USA (notice of allowance) and Japan (granted).

The product: Pitfalls & Risks to be considered

- Risk: Difficulties in gathering the estimated sample size.
  Proposed measure: Extend recruitment period, include additional centers.

- Risk: Insufficient quality of data.
  Proposed measure: Remote and on-site visits, verification of clinical data by the partners.

- Delays and difficulties with project progress.
  Proposed measure: Internal reporting, regular meetings…

Partnering Opportunities

CNIC and Fundació Clinic per la Recerca Biomèdica are interested in the collaboration with Industry to further continue the clinical trials development of this new therapeutic approach and the subsequent license agreement for use and exploitation.

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Laura Redondo: laura.redondo@cnic.es & Laura San Felipe: laura.sanfelipe@cnic.es (CNIC OTRI).

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EXCELENCIA SEVERO OCHOA

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Thank you!

Safety of mirabegron in patients

Author	Phase	Control (n)	Mirabegron (n)				Duration (months)	TEAEs Control vs. Mirabegron	Hypertension	QTc , arrhythmia	HR
			50 mg/d	100 mg/d	200 mg/d	300 mg/d					
Chapple[46]	2a	66			65 (100 bid)	65 (150 bid)	1	No diff. (36.4% vs. 39.2%).			Not relevant (5 bpm with 150 mg bid)
Chapple[47]	2b	166	167	168	166		3	No diff. (43.2% vs. 43.8-47.9%)	No diff.	No ECG diff. (including cQT).	2.15 bpm △HR with 100 mg & 4.66 mg with 200 mg.
Malik[51]	2		88	88	88		0.3			No QTc>480 ms or △QTc>60 ms.	Dose-dependent △HR.
Nitti[50]	3	440	442	433			3	No diff. (50.1% vs. 51.6% vs. 46.9%).	No diff. (6.6 % vs. 6.1% vs. 4.9%).	No QTc prolongation or arrhythmia.	
Khullar[49]	III	494	493	496			3	No diff. 43.3% vs. 42.8% vs 40.1%	No diff. 7.7 vs. 5.9 vs 5.4%	No △QTc. Arrhythmia 1% vs. 2.2% vs. 1.8%.	△HR of 0.8 bpm (CI 0-1.6) and 1.6 bpm (CI 0.8-2.4).
Herschorn[52]	III	433	440				3	No diff. OR=0.97 (0.68, 1.59)	No diff. OR= 1.07 (0,67, 1.71)	No diff. OR= 1.17 (0.52, 2.64)	
Chapple[48]	III	812 (toltero dine)	812	820			12	No diff. 62.6 vs. 59.7 vs. 61.3	No diff. 9.6 vs. 9.2 vs. 9.8%	△QTc 0.4 vs. 0.4 vs. 0.2 ms. Arrhythmia 6.0 vs. 3.9 vs. 4.1%.	Tachycardia 3.1% vs. 1.0% vs. 2.3%. △HR of 1.5 vs. 0.9 vs. 1.6 bpm.

Resumen ficha técnica mirabegron

- Con o sin alimentos.
- No efecto sobre la capacidad de conducir.
- No recomendada en IR terminal (<15 ml/min/1.73m2) o IH grave (Child C). En IR o IH moderada, valorar <dosis.
- No es necesario ajustar dosis con inhibidores del CYP2D6. No obstante se recomienda precaución (por estrecho margen terapéutico) en pacientes que toman flecainida y proparenona, antidepresivos tricíclicos, digoxina (monitorización de niveles) o dabigatran.
- Las complicaciones más frecuentes (entre 1/10 y 1/100) son taquicardia e infecciones urinarias.
- La incidencia de taquicardia con 50 mg (dosis de inicio) es de 1.2%, la de fibrilación auricular del 0.2%.
- El aumento máximo de FC con 50 mg fue de 6.7 lpm, y de 17.3 lpm con 200 mg.
- Con 50 mg el aumento de PA es de 1 mmHg.
- La dosis de 50 y 100 mg no tienen efecto sobre el QT. Hasta 200 mg no se ha evidenciado prolongación patológica del QT.

CRITERIOS DE INCLUSIÓN
Firma del consentimiento informado
≥18 años de edad.
IC con FEVI reducida, intermedia o preservada.
HP significativa (pre y post-capilar) determinada por cateterismo cardiaco: - PCP o PTDVI ≥ 15 mmHg - PAPm ≥25 mmHg; y: • RVP≥3 UW y/o gradiente diastólico≥7 mmHg, o • Gradiente transpulmonar ≥12 mmHg.
CF NYHA II o III.
Bajo tratamiento farmacológico óptimo
Condición estable (no ingresos ni cambios de medicación en últimos 30 días

CRITERIOS DE EXCLUSIÓN
Cirugía cardiaca no coronaria (p.e. cirugía valvular) o procedimiento terapéutico percutáneo no coronario (p.e. mitraclip) en los últimos 12 meses o programada.
Infarto de miocardio o revascularización coronaria en los últimos 3 meses.
Implante de marcapasos tricameral en los últimos 6 meses.
Taquicardia sinusal o fibrilación auricular con FC no controlada (FC>100 lpm).
HTA no controlada (PAs>180 o PAd>110 mmHg) o hipoTA (PAs<90 mmHg) sintomática.
Diagnóstico de miocardiopatía infiltrativa.
Mujeres pre-menopáusicas no histerectomizadas.
Supervivencia esperada <1 año por otra enfermedad diferente a la IC.
Insuficiencia renal grave (aclaramiento de creatinina <30 ml/min/1.73 m2).
Insuficiencia hepática significativa (transaminasas >3 el límite superior de normalidad).
Intervalo QT corregido en el ECG>430 seg en varones o >450 seg en mujeres.
Uso concomitante con vasodilatadores pulmonares específicos.
Tratamiento con digoxina, flecainida, propafenona, dabigatran, antidepresivos tricíclicos, u otros inhibidores del CYP2D6 (exceptuando betabloqueantes).
EPOC grave: FEV1/CVF <0.7 asociado a FEV1<50% del valor teórico.
Neumopatía restrictiva grave (CPT<50%).
Participación en otro ensayo clínico.
Alergia al mirabegron o alguno de los excipientes.

Algoritmo de titulación de dosis

Aumentar 50 mg	Si PA normal (PAS≥95 y ≤135) **Y** FC≤90 **Y** intervalo QT corregido <430 ms en hombres o <450 ms en mujeres **Y** analítica correcta **Y** ausencia de síntomas
Reducir (o suspender)	Si alguno de lo siguiente: hipoTA significativa (PAS<80 mmHg) ó HTA (PAS>145 mmHg) **O** FC>100 **O** QT prolongado (>430 ms en hombres o >450 ms en mujeres) **O** analítica incorrecta (empeoramiento de creatinina o aumento de transaminasas) **O** síntomas relacionados con la medicación.
Mantener igual	Si hipotensión leve (PAS≥80 y <90) ó hipertensión leve (PAS >135 y ≤145) **Y/O** FC 90-100 (y QT corregido <430 ms en hombres o <450 ms en mujeres **Y** analítica correcta)