β3-adrenergic receptor agonists for the treatment of chronic pulmonary hypertension

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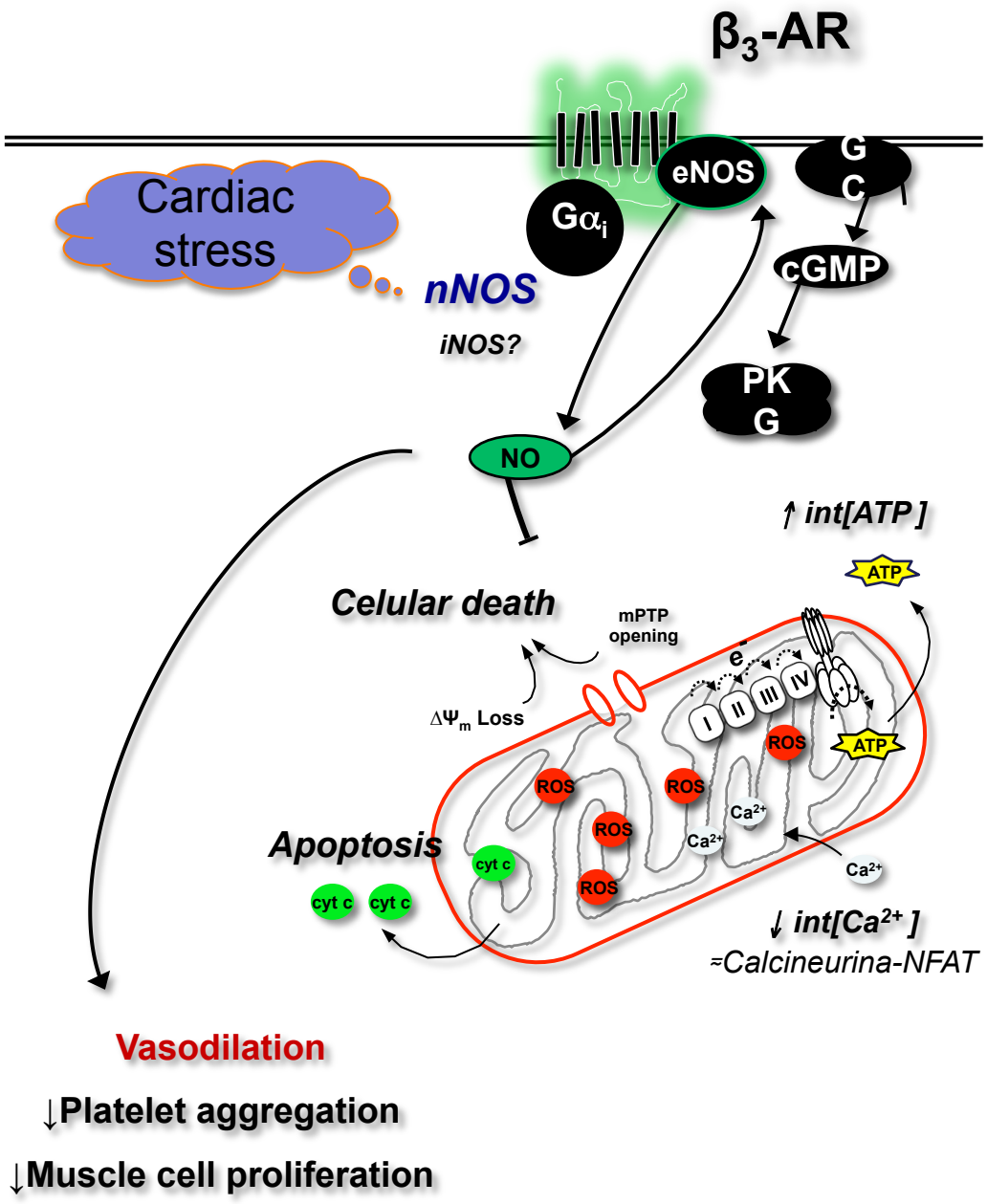
The Institutions

- **CNIC** and **Fundació Clinic per la Recerca Biomèdica** are both co-owners of the described invention.
- 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.
- 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

- Name: β3-adrenergic receptor agonists (β3AR agonists).
- Therapeutic area: β3AR agonists, particularly mirabegron (Betmiga®), are currently used for the treatment of hyperactive bladder syndrome. However, our research focuses in the use of β3AR agonists for the treatment of **chronic pulmonary hypertension.**
- Description: 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

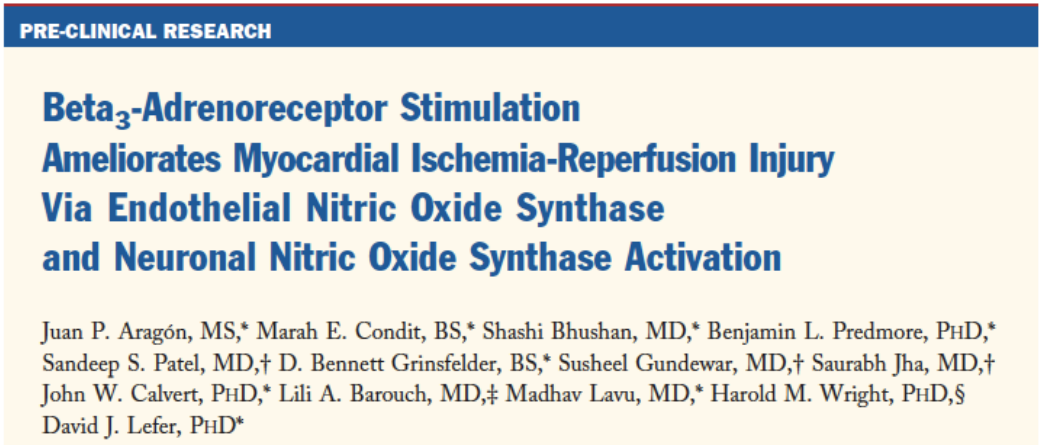


- β3AR are coupled to G proteins. The downstream pathway activated by β3AR includes nitric oxide synthase (NOS), NO-activated guanylyl cyclase and cGMP synthesis, and increased cAMP synthesis.
- Loss of cGMP and cAMP signaling is a hallmark in PH.
- Cyclic nucleotides are responsible for mediating endothelin-dependent dilatation and also have salutary actions on pulmonary vascular remodeling, fibrosis, and right ventricular (RV) function.

The product: Differential features facing the market

- Few therapies with high cost and limited beneficial effect are currently available for PAH (group 1 in the current PH classification), and no pharmacological therapy has been demonstrated to have a consistent effect in PH due to left heart disease (group 2) or chronic pulmonary disease (group 3), which are the most frequent causes of PH.
- If proven beneficial, β3AR agonists would be the first pharmacological treatment for PH due to left heart disease or pulmonary disease.
- β3AR agonists have demonstrated an additional cardioprotective effect (prevention of left ventricular fibrosis and remodeling) in experimental studies.
- 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: Current status of development

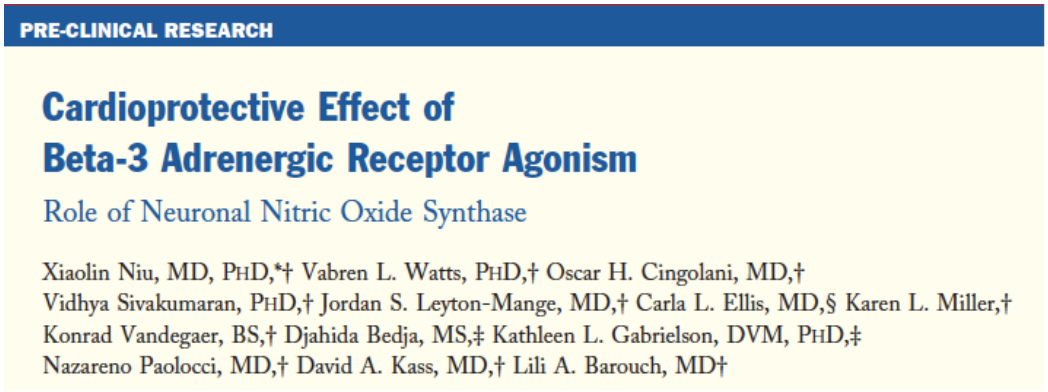


PRE-CLINICAL RESEARCH

Beta$_3$-Adrenoreceptor Stimulation Ameliorates Myocardial Ischemia-Reperfusion Injury Via Endothelial Nitric Oxide Synthase and Neuronal Nitric Oxide Synthase Activation

Juan P. Aragón, MS,* Marah E. Condit, BS,* Shashi Bhushan, MD,* Benjamin L. Predmore, PHD,* Sandeep S. Patel, MD,† D. Bennett Grinsfelder, BS,* Susheel Gundewar, MD,† Saurabh Jha, MD,† John W. Calvert, PHD,* Lili A. Barouch, MD,‡ Madhav Lavu, MD,* Harold M. Wright, PHD,§ David J. Lefer, PHD*

- Mice model of ischemia-reperfusion.
- ↓ infarct size.
- ↑NO.



PRE-CLINICAL RESEARCH

Cardioprotective Effect of Beta-3 Adrenergic Receptor Agonism

Role of Neuronal Nitric Oxide Synthase

Xiaolin Niu, MD, PHD,*† Vabren L. Watts, PHD,† Oscar H. Cingolani, MD,† Vidhya Sivakumaran, PHD,† Jordan S. Leyton-Mange, MD,† Carla L. Ellis, MD,§ Karen L. Miller,† Konrad Vandegaer, BS,† Djahida Bedja, MS,‡ Kathleen L. Gabrielson, DVM, PHD,‡ Nazareno Paolocci, MD,† David A. Kass, MD,† Lili A. Barouch, MD†

- Mice model of heart failure by aortic banding.
- ↓dilatation, hypertrophy and dysfunction of the left ventricle.
- ↑NO y ↓ROS.

Beta$_3$-AR stimulation causes **vasodilation in pulmonary vessels** in ex-vivo studies with rats and dogs (Dumas M. Eur J Pharmacol 1998; Tagaya E. Lung 1999).

The product: Current status of development

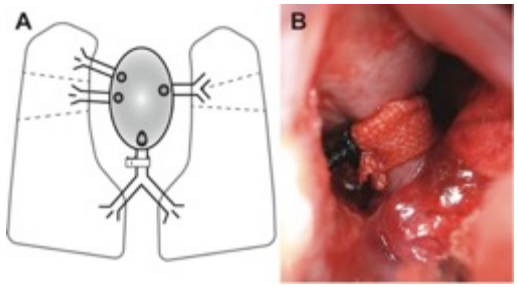
Own research in PH: methods

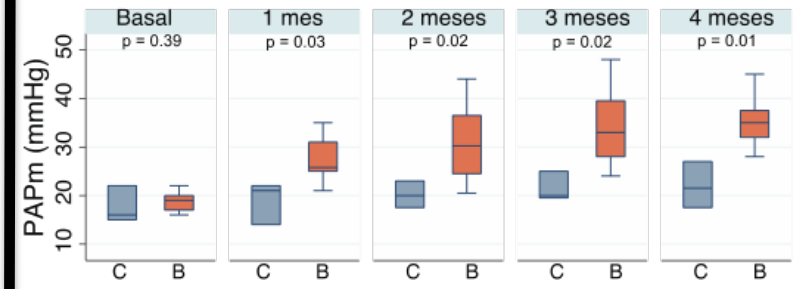
Effect in acute PH

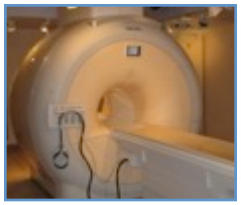
Acute pulmonary embolization

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

Effect in chronic PH



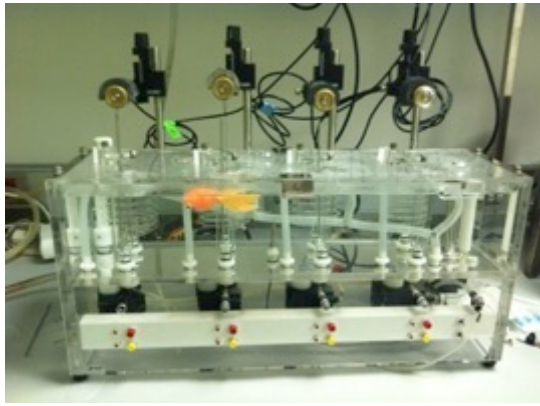




P27
Ki67

Human samples

Real-time PCR

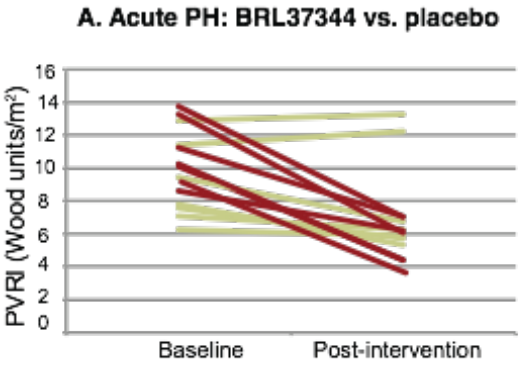


Organ bath studies

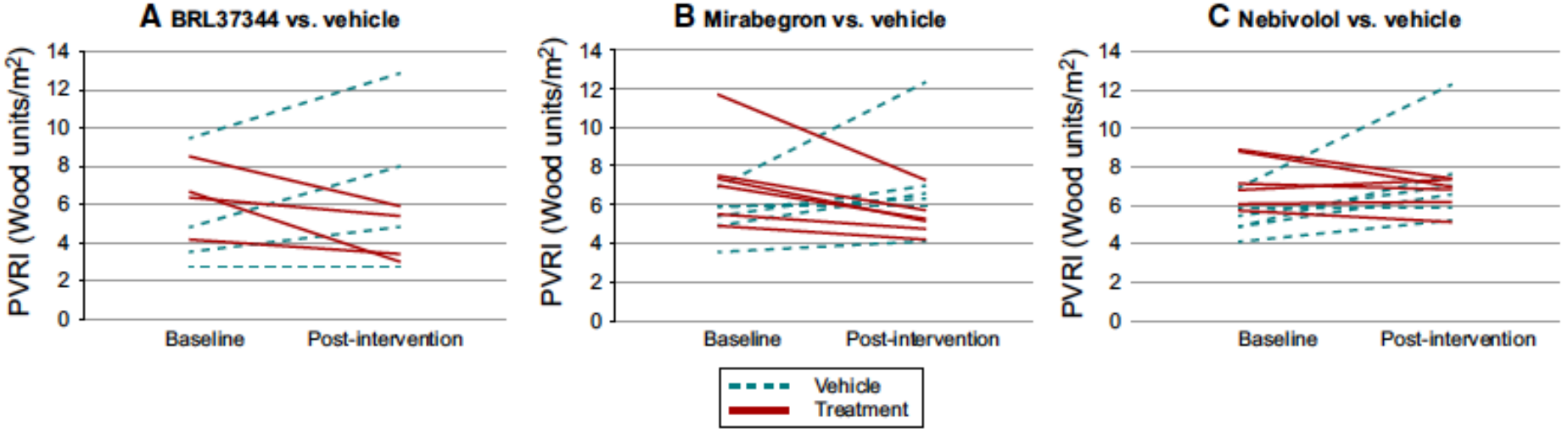
The product: Current status of development

Own research in PH: hemodynamic results

Objetivo 1



Objetivos 2 y 3



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The product: Current status of development

Own research in PH: right ventricular remodeling

	Baseline		Post-treatment		Change		
	Vehicle ($N = 10$)	β3AR agonist ($N = 10$)	Vehicle ($N = 10$)	β3AR agonist ($N = 10$)	Vehicle ($N = 10$)	β3AR agonist ($N = 10$)	p
Weight (kg)	47.2 (12.3)	42.7 (18.6)	57.3 (13.6)	54.0 (24.3)	10.2 (5.7)	12.0 (5.4)	0.481
HR (bpm)	67.5 (33.0)	79.0 (28.0)	73.0 (22.0)	85.5 (14.0)	4.5 (37.5)	15.0 (18.2)	0.631
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**
PA maximal area (cm^2)	7.0 (1.7)	7.8 (3.6)	7.0 (2.9)	7.5 (2.9)	−0.3 (1.7)	−0.6 (1.5)	0.089
PA minimal area (cm^2)	4.9 (2.2)	5.9 (3.2)	5.3 (2.4)	5.7 (2.4)	0.4 (1.5)	−0.3 (2.1)	0.075

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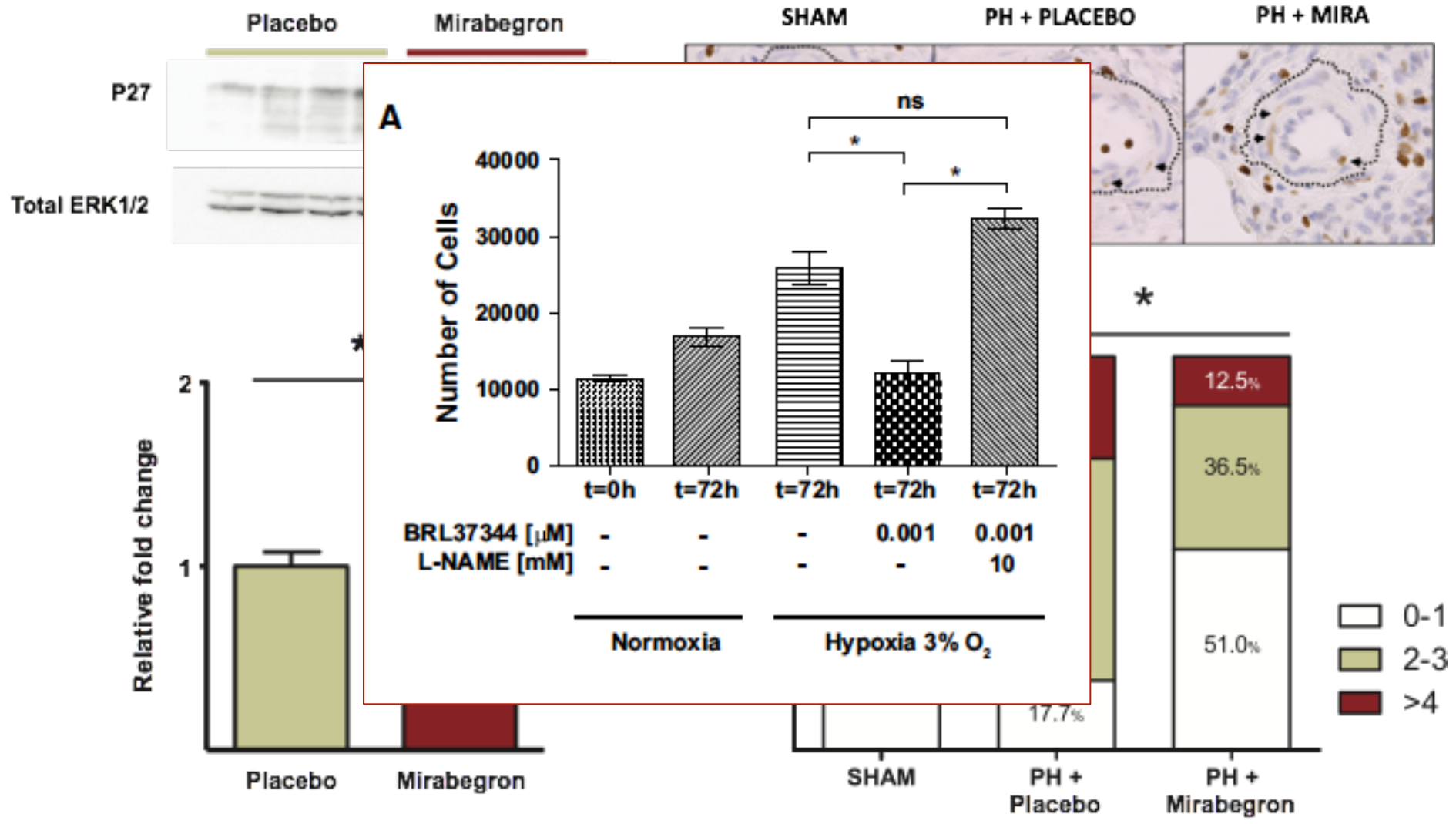
The product: Current status of development

Own research in PH: vascular remodeling



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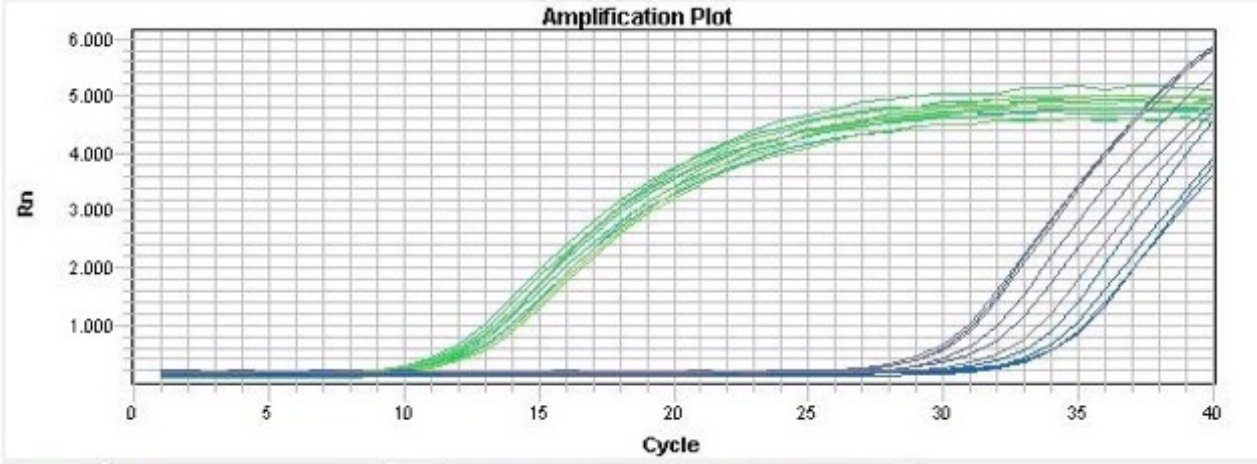
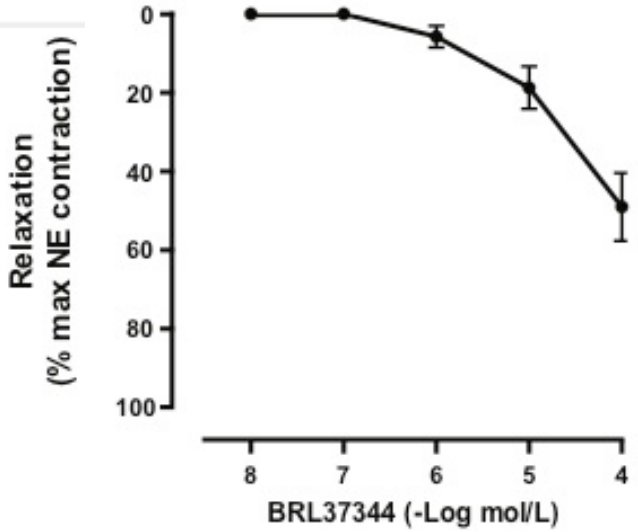
The product: Current status of development

Own research in PH: human arteries

Detección de receptores B3 en AP mediante PCRq



Vasodilatación dependiente de concentración



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The product: Current status of development

Own research in PH: Pilot clinical trial

La Marató 3

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

SPHERE-Heart failure

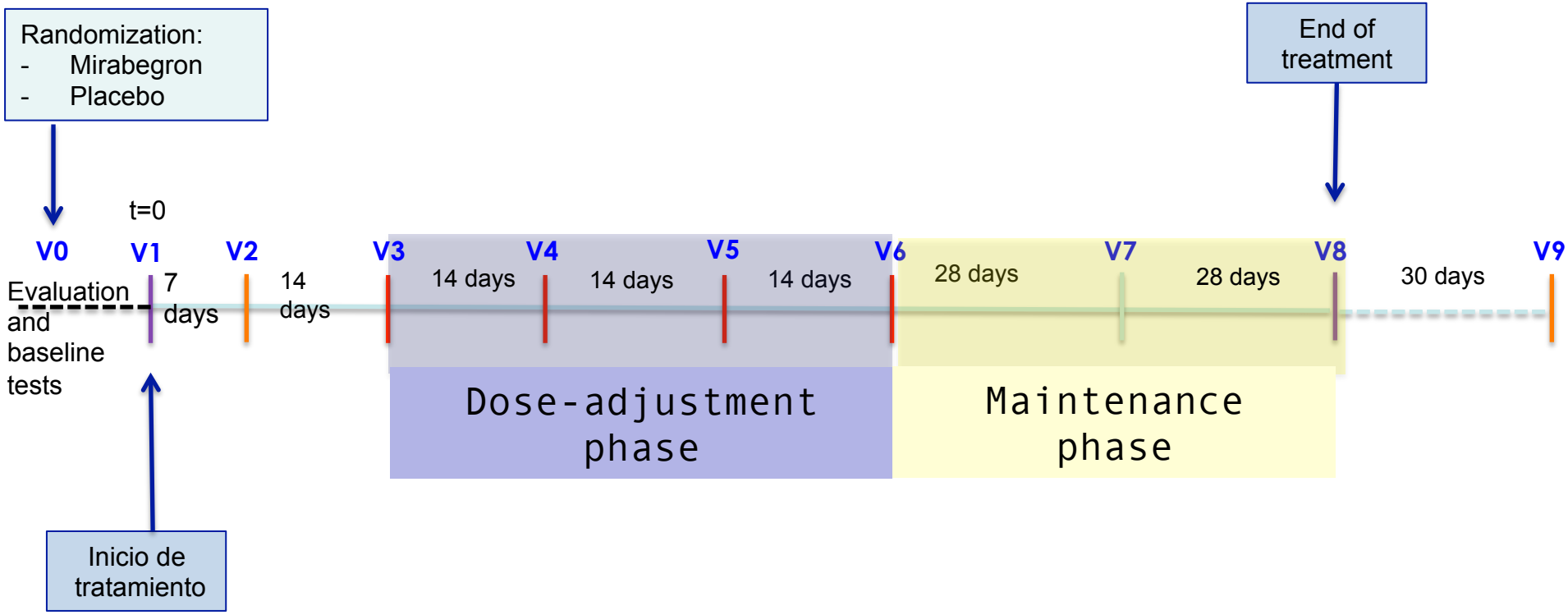
Aim

To evaluate the safety and security of mirabegron in patients with PH secondary to heart failure.

The product: Current status of development

- Randomized
- Double blinded
- N=80
- 4 centres

SPHERE-HF: design



- Clinical visit
- ECG
- 6MWT
- Blood test
- NT-proBNP
- Quality of life
- Ecocardiography
- CMR
- **Right heart cath**

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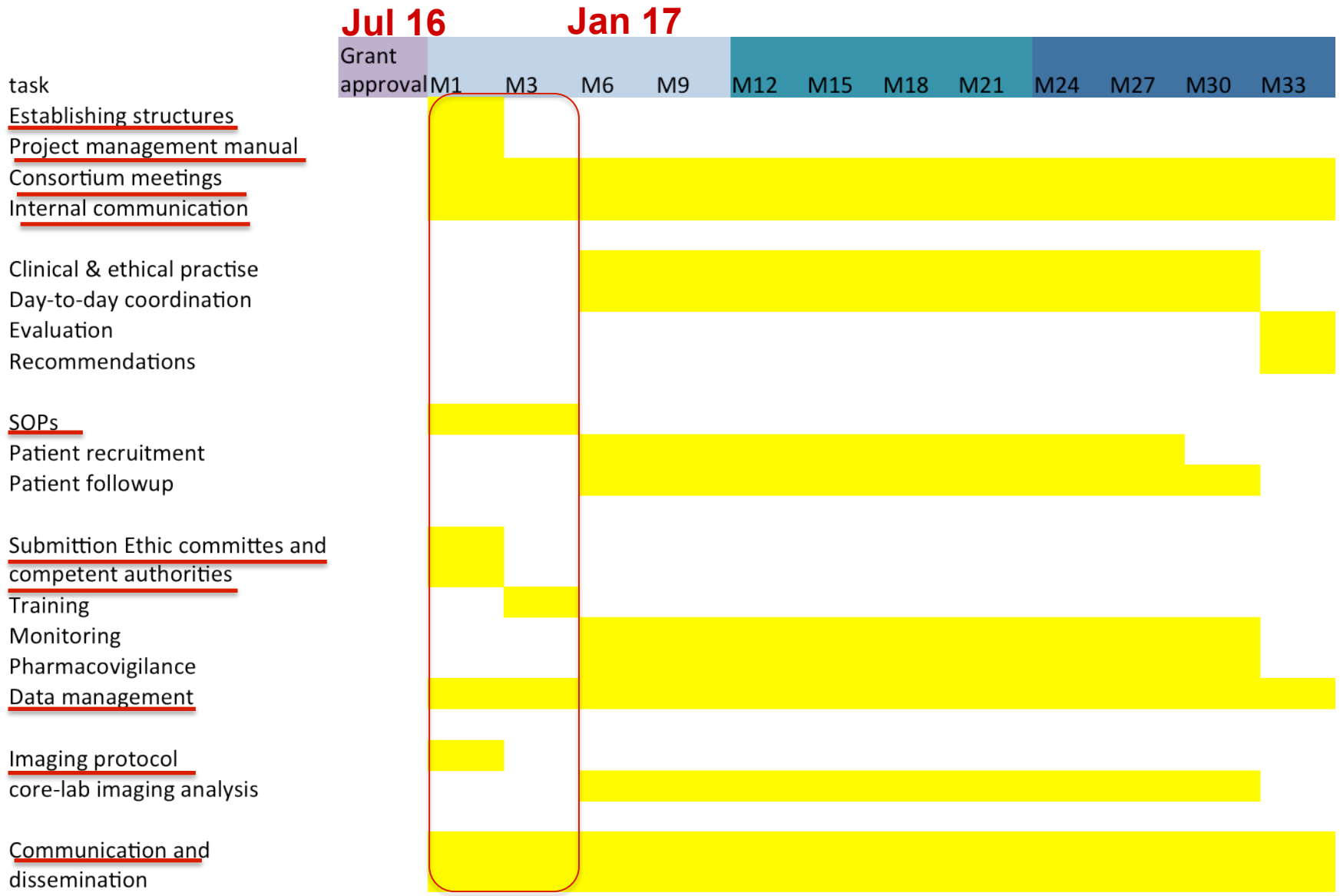
The product: Current status of development

SPHERE-HF: Gaant chart



The product: IPR protection

CNIC and Fundació Clinic per la Recerca Biomèdica, as co-owners of this invention, have filled in a related European patent application on August 29th, 2012 entitled “Beta-3 adrenoceptor agonists for the treatment of pulmonary hypertension” (WO 2014/033343). In 2015 this patent application entered into national/regional phases in Europe, USA and Japan.

The product: Pitfalls & Risks to be considered

Risk	Proposed risk-mitigation measures
Difficulties in gathering the estimated sample size	The scientific coordinator and Ips will activate their networks to increase the number of recruited patients. In the case that some institutions cannot recruit sufficient patients, the partners will able to recruit additional clinics to obtain the required number of patients; subcontracting to clinics will provide the flexibility required to adapt the trial network to potential problems faced in the field.
Quality of data	Frequent remote and on-site visits will be carried out to ensure that SPHERE trial protocols are strictly implemented. The clinical data obtained will be verified by the partners in terms of plausibility, completeness and consistency.
Delays and difficulties with project progress	Internal reporting, indicators for detection, regular meeting or teleconferences for corrective actions, recovery plan process.

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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