Clinical trial results:
A multi-centre randomized, placebo-controlled trial of mirabegron, a new beta3-adrenergic receptor agonist on the progression of left ventricular mass and diastolic function in patients with structural heart disease.

Summary

EudraCT number	2015-003146-75
Trial protocol	BE DE PT GR PL FR
Global end of trial date	16 March 2022

Results information

Result version number	v1 (current)
This version publication date	11 March 2023
First version publication date	11 March 2023
Summary attachment (see zip file)	BETA3_LVH, final report (Beta3_LVH Trial report final1.0_2023-02-21.pdf)

Trial information

Trial identification

Sponsor protocol code	BETA3_LVH

Additional study identifiers

ISRCTN number	ISRCTN65055502
ClinicalTrials.gov id (NCT number)	NCT02599480
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Université Catholique de Louvain
Sponsor organisation address	Place de L'Université 1, Louvain La Neuve, Belgium, 1348
Public contact	Nancy De Bremaeker, Luxembourg Institute of Health, Clinical & Epidemiological Investigation Center, 352 26970804, ecrin@lih.lu
Scientific contact	Nancy De Bremaeker, Luxembourg Institute of Health, Clinical & Epidemiological Investigation Center, 352 26970804, ecrin@lih.lu

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	13 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of mirabegron (a new β3-specific agonist) on change in left ventricular mass and/or changes in diastolic function after 12 months of treatment in patients with cardiac structural remodeling with or without symptoms of heart failure (maximum NYHA II).

Protection of trial subjects:

Trial subjects are seen at regular visits with a special focus on the observation of potential adverse reactions (high blood pressure, abnormal liver and/or kidney laboratory parameters) in addition to routine (S)AE observation and clinical course of the underlying disease.

Background therapy:

Standard of care

Evidence for comparator:

In the BETA3_LVH trial, Betmiga is given in addition to standard of care treatment for patients with underlying cardiac disease at an early stage. Since the use of Betmiga in preventing further cardiac remodeling so far is not proven, the use of placebo as comparator is ethically justified.

Actual start date of recruitment	12 September 2016
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	Poland: 82
Country: Number of subjects enrolled	Portugal: 23
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 100
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Italy: 41
Worldwide total number of subjects	296
EEA total number of subjects	285

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)	152
From 65 to 84 years	142
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Between September 2019 and March 2022, 380 patients were registered and 296 patients randomised for the BETA3_LVH trial.

Pre-assignment

Screening details:

A total of 380 patients were screened, from which 296 patients were enrolled and randomised.

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, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirabegron

Arm description:

Administration of 50 mg mirabegron once daily per os (Betmiga®, Astellas Pharma) over a period of 12 months.

Arm type	Experimental
Investigational medicinal product name	Betmiga
Investigational medicinal product code	ATC code: G04BD12
Other name	Mirabegron
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

50 mg/day

Arm title	Placebo

Arm description:

Administration of placebo once daily per os over a period of 12 months.

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

Dosage and administration details:

50 mg/day

Number of subjects in period 1	Mirabegron	Placebo
Started	147	149
Completed	128	133
Not completed	19	16
Covid 19 restrictions	-	1
Consent withdrawn by subject	8	10
Adverse event, non-fatal	5	3
Lost to follow-up	6	2

Baseline characteristics

Reporting groups	
Reporting group title	Mirabegron
Reporting group description:	
Administration of 50 mg mirabegron once daily per os (Betmiga®, Astellas Pharma) over a period of 12 months.	
Reporting group title	Placebo
Reporting group description:	
Administration of placebo once daily per os over a period of 12 months.	

Reporting group values	Mirabegron	Placebo	Total
Number of subjects	147	149	296
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	64	62.2	
standard deviation	± 10.2	± 10.9	-
Gender categorical			
Units: Subjects			
Female	31	37	68
Male	116	112	228

End points

End points reporting groups

Reporting group title	Mirabegron
Reporting group description:	
Administration of 50 mg mirabegron once daily per os (Betmiga®, Astellas Pharma) over a period of 12 months.	
Reporting group title	Placebo
Reporting group description:	
Administration of placebo once daily per os over a period of 12 months.	

Primary: Left ventricular mass index

End point title	Left ventricular mass index
End point description:	
Two equally ranked, primary endpoints have been defined in order to assess both structural and functional aspects of left ventricular remodeling: i.e. change in left ventricular mass index (LVMI in g/m2, defined as left ventricular mass divided by body surface) measured by cardiac MRI at baseline, 6 and 12 months after randomisation. Cardiac MRI was performed locally according to a standardized protocol, and LVMI was measured in the central MRI core lab	
End point type	Primary
End point timeframe:	
12 months	

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148[1]		
Units: g/m2				
arithmetic mean (standard deviation)	61.2 (± 12.32)	57.7 (± 10.77)		

Notes:

[1] - 1 was excluded from primary endpoint LVMI
(all measurements missing)

Statistical analyses

Statistical analysis title	LVMI primary
Statistical analysis description:	
Analyses of both primary endpoints are identically structured; mean changes from baseline mean were analyzed using a repeated measurement linear mixed model without intercept containing the fixed, categorical effects of visit (baseline, 6 mo, 12 mo), treatment (verum / placebo), treatment by visit interaction, atrial fibrillation (yes / no), diabetes mellitus (yes / no), as well as a patient-specific, visit random effect (3-dim normal with a general unstructured variance covariance matrix).	
Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	repeated measurement linear mixed model
Parameter estimate	Mean difference (final values)
Point estimate	1.295
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.152
upper limit	2.742

Primary: E/e`

End point title	E/e`

End point description:

Two equally ranked, primary endpoints have been defined in order to assess both structural and functional aspects of left ventricular remodeling: ii. change in diastolic function, assessed as the ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity (E/e') measured by echocardiography at baseline, 6 and 12 months after randomisation. Echocardiography was performed locally according to a standardized protocol, and was measured in the central echocardiography core lab.

End point type	Primary

End point timeframe:

12 months

End point values	Mirabegron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143[2]	147[3]		
Units: ratio				
arithmetic mean (standard deviation)	9.11 (± 2.64)	9.74 (± 3.46)		

Notes:

[2] - 4 were excluded from primary endpoint E/e´ (all measurements missing)

[3] - 2 were excluded from primary endpoint E/e´ (all measurements missing)

Statistical analyses

Statistical analysis title	E/e´primary

Statistical analysis description:

mean changes from baseline mean were analyzed using a repeated measurement linear mixed model without intercept containing the fixed, categorical effects of visit (baseline, 6 months, 12 months), treatment (verum / placebo), treatment by visit interaction, atrial fibrillation (yes / no), diabetes mellitus (yes / no), as well as a patient-specific, visit random effect (3-dimensional normal with a general unstructured variance covariance matrix).

Comparison groups	Mirabegron v Placebo

Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.597
Method	repeated measurement linear mixed model
Parameter estimate	Mean difference (final values)
Point estimate	-0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.694
upper limit	0.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from baseline to 4 weeks after end of treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Mirabegron
Reporting group description: Administration of 50 mg mirabegron once daily per os (Betmiga®, Astellas Pharma) over a period of 12 months.	
Reporting group title	Placebo
Reporting group description: Administration of placebo once daily per os over a period of 12 months.	

Serious adverse events	Mirabegron	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 148 (12.84%)	22 / 148 (14.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal gland cancer			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granular cell tumour			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	2 / 148 (1.35%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic hypertension			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac ablation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint arthroplasty			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain management			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia repair			

subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 148 (1.35%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiocardiogram			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 148 (0.68%)	3 / 148 (2.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure systolic increased			
subjects affected / exposed	2 / 148 (1.35%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Glomerular filtration rate abnormal			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 148 (1.35%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 148 (2.03%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 148 (0.68%)	3 / 148 (2.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 148 (0.68%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Lens dislocation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric polyps			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hepatitis A			

subjects affected / exposed	1 / 148 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 148 (0.00%)	2 / 148 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Mirabegron	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 148 (20.95%)	37 / 148 (25.00%)	
Investigations			
Blood pressure diastolic increased			
subjects affected / exposed	7 / 148 (4.73%)	8 / 148 (5.41%)	
occurrences (all)	12	8	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 148 (6.76%)	9 / 148 (6.08%)	
occurrences (all)	10	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 148 (5.41%)	10 / 148 (6.76%)	
occurrences (all)	8	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 148 (4.05%)	10 / 148 (6.76%)	
occurrences (all)	7	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2016	o correction of mistakes, more precise description of procedures o addition of a new chapter, describing a scientific sub-project for genetic tests regarding heart failure o adaptation of the selection criteria to the current guidelines and addition of a selection criterion: „Patients placed in an institution by official or court order" o resulting in trial protocol version final 5.0 of 03.11.2016 o new IMPD (version 3 of 10.10.2016)
18 September 2017	o addition of pO2 and pCO2 measurements from venous blood samples for the calculation of nitrosylated haemoglobin o specification of the procedures to be followed for premature termination of trial therapy for individual patients o addition of a new trial site o minor mistakes were corrected o resulting in trial protocol version final 6.0 of 31.08.2017
23 October 2019	o extension of the recruitment period to 53 months o change in reference safety information (SmPC from April 09th, 2019) o closure of the University of Oxford as recruiting trial site o resulting in trial protocol version final 7.0 of 21.10.2019

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29932311