EU Clinical Trials Register

Clinical trial results:
A multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to evaluate the effects of macitentan on exercise capacity in subjects with Eisenmenger Syndrome

Summary

EudraCT number	2012-003335-33
Trial protocol	GB IT BG BE DE PT NL AT ES HU CZ GR
Global end of trial date	01 December 2016

Results information

Result version number	v1 (current)
This version publication date	24 June 2017
First version publication date	24 June 2017

Trial information

Trial identification

Sponsor protocol code	AC-055-305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01743001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestr. 16, Allschwil, Switzerland, 4123
Public contact	Actelion Pharmaceuticals Ltd, clinical trial disclosure desk, clinical-trials-disclosure@actelion.com
Scientific contact	Actelion Pharmaceuticals Ltd, clinical trial disclosure desk, clinical-trials-disclosure@actelion.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of macitentan on exercise capacity in subjects with Eisenmenger Syndrome

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation.
The study was conducted in compliance with the principles of the 'Declaration of Helsinki', the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the clinical research was conducted.
Both Actelion and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests.
Prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study, written informed consent was obtained from each participating adult subject (including DS subjects who were able to consent), as well as from the parent(s) or legal representative(s) of each participating minor, and from the parent(s)/legal representative(s) or caregiver(s) of each participating subject with DS, who was not able to personally read and sign the informed consent. Additionally, written assent was obtained from each minor and each DS subject who was unable to give written consent. All subjects who participated in the hemodynamic sub-study were required to sign a separate informed consent form (ICF). Informed consent/assent was obtained in accordance with the national laws or regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2013
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	China: 70
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Vietnam: 16
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Mexico: 30

Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	226
EEA total number of subjects	61

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)	15
Adults (18-64 years)	211
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

71 sites in 26 countries

Pre-assignment

Screening details:

The screening period lasted a maximum of 30 days from Visit 1 up to Randomization (Visit 2). Total of 319 screened subjects.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan

Arm description:

Macitentan

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg, once-daily, oral, film-coated tablet

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, once-daily, oral, film-coated tablet

Number of subjects in period 1	Macitentan	Placebo
Started	114	112
Completed	114	112

Period 2

Period 2 title	Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan

Arm description:

Subjects receive macitentan 10 mg oral tablet once daily

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg, once-daily, oral, film-coated tablet

Arm title	Placebo

Arm description:

Subjects receive macitentan-matching placebo oral tablet once daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, once-daily, oral, film-coated tablet

Number of subjects in period 2	Macitentan	Placebo
Started	114	112
Completed	111	112
Not completed	3	0
Adverse event, serious fatal	1	-
Physician decision	1	-
Pregnancy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Macitentan
Reporting group description:	
Macitentan	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	Macitentan	Placebo	Total
Number of subjects	114	112	226
Age categorical			
Full analysis set (FAS)			
Units: Subjects			
Adolescents (12-17 years)	13	2	15
Adults (18 - 55 years)	90	105	195
Adults >= 55 years	11	5	16
Age continuous			
Full analysis set (FAS)			
Units: years			
median	33	31	
full range (min-max)	12 to 82	13 to 62	-
Gender categorical			
Units: Subjects			
Female	82	68	150
Male	32	44	76

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) included all subjects from the SCR allocated to a randomized study treatment. Subjects were evaluated according to the study treatment to which they were assigned. All available data were taken into account for the analysis.

Subject analysis set title	Per-protocol analysis set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol analysis set (PPS) comprised data from all subjects included in the FAS without major protocol deviations or conditions, which might have affected the evaluation of the effect of the study treatment on the primary efficacy endpoint.

Reporting group values	Full analysis set (FAS)	Per-protocol analysis set (PPS)	
Number of subjects	226	200	
Age categorical			
Full analysis set (FAS)			
Units: Subjects			

Adolescents (12-17 years)	15	13	
Adults (18 - 55 years)	195	176	
Adults >= 55 years	16	11	

Age continuous			
Full analysis set (FAS)			
Units: years			
median	32	32	
full range (min-max)	12 to 82	12 to 82	
Gender categorical			
Units: Subjects			
Female	150	132	
Male	76	68	

End points

End points reporting groups

Reporting group title	Macitentan
Reporting group description:	
Macitentan	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Macitentan
Reporting group description:	
Subjects receive macitentan 10 mg oral tablet once daily	
Reporting group title	Placebo
Reporting group description:	
Subjects receive macitentan-matching placebo oral tablet once daily	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	

The full analysis set (FAS) included all subjects from the SCR allocated to a randomized study treatment. Subjects were evaluated according to the study treatment to which they were assigned. All available data were taken into account for the analysis.

Subject analysis set title	Per-protocol analysis set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	

The per-protocol analysis set (PPS) comprised data from all subjects included in the FAS without major protocol deviations or conditions, which might have affected the evaluation of the effect of the study treatment on the primary efficacy endpoint.

Primary: Change from baseline to Week 16 in exercise capacity, as measured by 6MWD

End point title	Change from baseline to Week 16 in exercise capacity, as measured by 6MWD
End point description:	
End point type	Primary
End point timeframe:	
From baseline to Week 16	

End point values	Macitentan	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	114	112	0[1]	
Units: meter				
arithmetic mean (standard deviation)	18.3 (± 84.4)	19.7 (± 53)	()	

Notes:

[1] - NA

Statistical analyses

Statistical analysis title	Main analysis

Statistical analysis description:

ANCOVA for the change from baseline to Week 16 including randomized treatment group, presence of DS (yes/no), WHO FC (II vs III/IV) and baseline 6MWD value as covariates

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.612
Method	ANCOVA
Parameter estimate	Least-square mean difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	13.5
Variability estimate	Standard error of the mean
Dispersion value	9.2

Notes:

[2] - ANCOVA

Secondary: Change from baseline to Week 16 in WHO functional class

End point title	Change from baseline to Week 16 in WHO functional class

End point description:

WHO functional class dichotomized as improvement from baseline to Week 16 'Yes' (i.e., shift to lower class [e.g., from III to II]) or 'No' (i.e., shift to higher class [e.g., from III to IV] or unchanged).

End point type	Secondary

End point timeframe:

From baseline to Week 16

End point values	Macitentan	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	114	112	0[3]	
Units: Participants	10	16		

Notes:

[3] - NA

Statistical analyses

Statistical analysis title	Main analysis

Statistical analysis description:

Logistic regression model for the improvement from baseline to Week 16 including randomized treatment group and location of cardiac defect (pre-tricuspid/ post-tricuspid) as categorical factors

Comparison groups	Macitentan v Placebo

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.145
Method	Wlad chi-square test
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	1.24

Secondary: Change from baseline to Week 16 in dyspnea (assessed by the Borg dyspnea index)

End point title	Change from baseline to Week 16 in dyspnea (assessed by the Borg dyspnea index)
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to Week 16	

End point values	Macitentan	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	114	112	0[4]	
Units: Index				
arithmetic mean (standard deviation)				
Index	-0.22 (± 1.56)	-0.29 (± 1.5)	()	

Notes:

[4] - NA

Statistical analyses

Statistical analysis title	Main analysis
Statistical analysis description:	

ANCOVA for the change from baseline to Week 16 including randomized treatment group and location of cardiac defect (pre-tricuspid/ post-tricuspid) and baseline Borg dyspnea index as covariates

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8456 [5]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Macitentan - Placebo
Point estimate	0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.46

Notes:

[5] - P-value Wilcoxon rank sum test

Secondary: Change from baseline to Week 16 in quality of life (assessed by the SF-36 questionnaire)

End point title	Change from baseline to Week 16 in quality of life (assessed by the SF-36 questionnaire)

End point description:

SF-36 PHYSICAL FUNCTIONING, SF-36 ROLE-PHYSICAL, SF-36 PAIN INDEX, SF-36 GENERAL HEALTH PERCEPTIONS, SF-36 VITALITY, SF-36 SOCIAL FUNCTIONING, SF-36 ROLE-EMOTIONAL, and SF-36 MENTAL HEALTH INDEX

End point type	Secondary

End point timeframe:

From baseline to Week 16

End point values	Macitentan	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	99	0[6]	
Units: Scores				
least squares mean (standard error)				
SF-36 PHYSICAL FUNCTIONING	4.4 (± 1.5)	5.3 (± 1.6)	()	
SF-36 ROLE-PHYSICAL	5.7 (± 2)	7.2 (± 2.1)	()	
SF-36 PAIN INDEX	3.2 (± 2.3)	3.1 (± 2.4)	()	
SF-36 GENERAL HEALTH PERCEPTIONS	5 (± 1.6)	1.9 (± 1.7)	()	
SF-36 VITALITY	6.9 (± 1.6)	5.8 (± 1.7)	()	
SF-36 SOCIAL FUNCTIONING	1.3 (± 2.2)	2.6 (± 2.3)	()	
SF-36 ROLE-EMOTIONAL	1.7 (± 2.2)	4.6 (± 2.4)	()	
SF-36 MENTAL HEALTH INDEX	2.8 (± 1.5)	5.1 (± 1.6)	()	

Notes:

[6] - NA

Statistical analyses

Statistical analysis title	SF-36 PHYSICAL FUNCTIONING
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other[7]
Method	ANCOVA
Parameter estimate	Macitentan - Placebo
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	3.1
Variability estimate	Standard error of the mean
Dispersion value	2.1

Notes:

[7] - Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

Statistical analysis title	SF-36 ROLE-PHYSICAL

Statistical analysis description:

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Macitentan - Placebo
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	2.7

Statistical analysis title	SF-36 PAIN INDEX

Statistical analysis description:

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Macitentan - Placebo
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	6.2
Variability estimate	Standard error of the mean
Dispersion value	3.1

Statistical analysis title	SF-36 GENERAL HEALTH PERCEPTIONS
Statistical analysis description:	
Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).	
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Macitentan - Placebo
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	7.3
Variability estimate	Standard error of the mean
Dispersion value	2.2

Statistical analysis title	SF-36 VITALITY
Statistical analysis description:	
Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).	
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Macitentan - Placebo
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	2.1

Statistical analysis title	SF-36 SOCIAL FUNCTIONING
Statistical analysis description:	
Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).	
Comparison groups	Macitentan v Placebo

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Macitentan - Placebo
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	4.4
Variability estimate	Standard error of the mean
Dispersion value	2.9

Statistical analysis title	SF-36 ROLE-EMOTIONAL

Statistical analysis description:

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Macitentan - Placebo
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	3

Statistical analysis title	SF-36 MENTAL HEALTH INDEX

Statistical analysis description:

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Macitentan - Placebo
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	1.8

Variability estimate	Standard error of the mean
Dispersion value	2.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study treatment initiation up to 30 days after study treatment discontinuation

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Placebo

Reporting group description:

112 subjects were exposed to Placebo for 15.96 weeks on average

Reporting group title	Macitentan_10_mg

Reporting group description:

114 subjects were exposed to Macitentan 10mg for 15.93 weeks on average

Serious adverse events	Placebo	Macitentan_10_mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 112 (1.79%)	7 / 114 (6.14%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 112 (0.00%)	3 / 114 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transient ischaemic attack		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders		
Respiratory failure		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Renal and urinary disorders		
Acute kidney injury		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infections and infestations		
Endocarditis		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	0 / 112 (0.00%)	2 / 114 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Septic shock		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)
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	Placebo	Macitentan_10_mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 112 (26.79%)	31 / 114 (27.19%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 112 (4.46%)	13 / 114 (11.40%)	
occurrences (all)	5	15	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	6 / 112 (5.36%)	0 / 114 (0.00%)	
occurrences (all)	8	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 112 (2.68%)	6 / 114 (5.26%)	
occurrences (all)	3	6	
Nasopharyngitis			
subjects affected / exposed	14 / 112 (12.50%)	3 / 114 (2.63%)	
occurrences (all)	16	4	
Upper respiratory tract infection			
subjects affected / exposed	7 / 112 (6.25%)	11 / 114 (9.65%)	
occurrences (all)	10	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2013	Amendment 1 - Changes included: - Efficacy as well as safety and tolerability endpoints sections were revised; - The main efficacy analysis plan was updated - The alternative analysis methods described initially for the main analysis, in case assumptions of normality and homogeneity of variance are not met following an assessment, were changed to a sensitivity analysis. - The overall study design and plan were modified to allow those subjects who did not meet the eligibility criteria for the sub-study to be considered for the main study on a case-by-case basis. - Exclusion criterion 5 concerning systolic blood pressure was updated - Other changes.
13 March 2014	Global Amendment 2 - Changes included: - The study design and eligibility criteria were modified to allow the participation of additional subjects with more complex cardiac defects, including those with Down Syndrom, - Inclusion criterion 3 was revised; - Cardiac catheterization requirements (inclusion criterion 4) were updated; - The limit of variance between the 2 6MWT at screening was increased to 15% (inclusion criterion 6). - Exclusion criterion 1 was revised to rule out (1) other causes of pulmonary hypertension - Other changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no significant limitations of the trial.

Notes: