



Clinical trial results:

A Multicenter, Single-arm, Open-label, Phase 3b Study to Assess the Effects of Switching From Flolan® to ACT-385781A in Patients with Pulmonary Arterial Hypertension

Summary

EudraCT number	2010-018322-40
Trial protocol	FR BE NL ES IT
Global end of trial date	02 February 2012

Results information

Result version number	v1 (current)
This version publication date	17 June 2017
First version publication date	17 June 2017

Trial information

Trial identification

Sponsor protocol code	AC-066A301
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01431716
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Global Scientific Information, Actelion Pharmaceuticals Ltd, medinfo@actelion.com
Scientific contact	Global Scientific Information, Actelion Pharmaceuticals Ltd, medinfo@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2012
Global end of trial reached?	Yes
Global end of trial date	02 February 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the change in cardiac hemodynamics from baseline to 3-month following switch from Flolan® to EFI in patients with pulmonary arterial hypertension (PAH).

To evaluate the safety and tolerability of switching from Flolan® to EFI in patients with PAH.

Protection of trial subjects:

The clinical trial was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

The protocol, the amendments and any material provided to the patient (such as a patient information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC before the study was started.

The investigator ensured that this study was conducted in full compliance with the principles of the 'Declaration of Helsinki' and its amendments, and with the laws and regulations of the country in which the clinical research was conducted. A copy of the Declaration of Helsinki and International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines was provided to each investigational site.

Written informed consent was obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the objectives, methods, and potential hazards of the study.

During the 90-day treatment period, there were visits to the clinic on week 1, 4, and 12, and phone calls from the clinic to the patient on weeks 2, 3, 6, 8, 10 and 16, and on Day 91.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	41
EEA total number of subjects	33

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)	38
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled at eight centers in the European Union and Canada. First patient, first visit was 15 March 2011 and last patient, last visit was 2 February 2012.

Pre-assignment

Screening details:

Patients must have PAH and have been treated with Flolan for at least 12 months and on a stable dose for at least 3 months prior to enrollment. There was a screening period of up to 14 days.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Epoprostenol for injection (EFI/ACT-385781A)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Epoprostenol for Injection
Investigational medicinal product code	ACT-385781A
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:
continuous intravenous

Number of subjects in period 1	Epoprostenol for injection (EFI/ACT-385781A)
Started	41
Completed	41

Baseline characteristics

Reporting groups

Reporting group title	Overall study
-----------------------	---------------

Reporting group description:

Treatment

Reporting group values	Overall study	Total	
Number of subjects	41	41	
Age categorical			
Age categorical description			
Units: participants			
<=18 years	0	0	
Between 18 and 65 years	38	38	
>=65 years	3	3	
Age continuous			
Age continuous description			
Units: years			
median	46		
full range (min-max)	23 to 78	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	30	30	
Male	11	11	
Race/Ethnicity, Customized			
Units: Subjects			
White/Caucasian	18	18	
Black	2	2	
Asian	1	1	
Not Collected	20	20	
Region of Enrollment			
Units: Subjects			
France	20	20	
Canada	8	8	
Spain	2	2	
Belgium	5	5	
Netherlands	4	4	
Italy	2	2	

Subject analysis sets

Subject analysis set title	All-treated set
----------------------------	-----------------

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

Patients with at least one dose of study medication

Subject analysis set title	Per-protocol set
----------------------------	------------------

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

Treated patients who had a pulmonary vascular resistance (PVR) value at baseline and at end of treatment (EOT) and who did not deviate from the protocol in a way that might have affected the evaluation of PVR. This set was used for a supportive analysis of PVR only.

Reporting group values	All-treated set	Per-protocol set	
Number of subjects	41	27	
Age categorical			
Age categorical description			
Units: participants			
<=18 years	0		
Between 18 and 65 years	38		
>=65 years	3		
Age continuous			
Age continuous description			
Units: years			
median	46		
full range (min-max)	23 to 78		
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	30		
Male	11		
Race/Ethnicity, Customized			
Units: Subjects			
White/Caucasian	18		
Black	2		
Asian	1		
Not Collected	20		
Region of Enrollment			
Units: Subjects			
France	20	14	
Canada	8	7	
Spain	2	1	
Belgium	5	2	
Netherlands	4	1	
Italy	2	2	

End points

End points reporting groups

Reporting group title	Epoprostenol for injection (EFI/ACT-385781A)
Reporting group description: -	
Subject analysis set title	All-treated set
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients with at least one dose of study medication	
Subject analysis set title	Per-protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Treated patients who had a pulmonary vascular resistance (PVR) value at baseline and at end of treatment (EOT) and who did not deviate from the protocol in a way that might have affected the evaluation of PVR. This set was used for a supportive analysis of PVR only.	

Primary: Not applicable

End point title	Not applicable ^[1]
End point description:	
No primary endpoint was defined. As it is an exploratory study, all efficacy endpoints were considered as exploratory endpoints	
End point type	Primary
End point timeframe:	
Not applicable	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was an exploratory study. No statistical analysis has been specified.

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[2]			
Units: Not applicable				

Notes:

[2] - Not applicable

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in PVR from baseline to EOT.

End point title	Change in PVR from baseline to EOT.
End point description:	
Right heart catheterization was performed for cardiac hemodynamic assessment at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.	
End point type	Other pre-specified
End point timeframe:	
From baseline to 3 months	

End point values	Epoprostenol for injection (EFI/ACT-385781A)	All-treated set	Per-protocol set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	36	36	27	
Units: dyn/sec/cm ⁵				
arithmetic mean (standard deviation)				
Baseline	595.7 (± 237.14)	595.7 (± 237.14)	587.61 (± 240.71)	
End of treatment	587.66 (± 248.44)	587.66 (± 248.44)	602.12 (± 247.99)	
Change from baseline	-8.04 (± 116.83)	-8.04 (± 116.83)	14.52 (± 111.27)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in total pulmonary resistance from baseline to EOT.

End point title	Change in total pulmonary resistance from baseline to EOT.
-----------------	--

End point description:

Right heart catheterization was performed for cardiac hemodynamic assessment at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: dyn/sec/cm ⁵				
arithmetic mean (standard deviation)				
Baseline	752.44 (± 260.91)			
End of treatment	757.51 (± 296.82)			
Change from baseline	5.07 (± 128.89)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in mean pulmonary arterial pressure from baseline to EOT.

End point title	Change in mean pulmonary arterial pressure from baseline to EOT.
-----------------	--

End point description:

Right heart catheterization was performed for cardiac hemodynamic assessment at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	51.9 (± 11.5)			
End of treatment	51.7 (± 12.8)			
Change from baseline	-0.2 (± 7)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in mean right atrial pressure from baseline to EOT.

End point title	Change in mean right atrial pressure from baseline to EOT.
-----------------	--

End point description:

Right heart catheterization was performed for cardiac hemodynamic assessment at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	7.9 (± 4.6)			
End of treatment	7.1 (± 4.6)			
Change from baseline	-0.8 (± 3.6)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in pulmonary capillary wedge pressure from baseline to EOT.

End point title	Change in pulmonary capillary wedge pressure from baseline to EOT.
End point description:	
Right heart catheterization was performed for cardiac hemodynamic assessment at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.	
End point type	Other pre-specified
End point timeframe:	
Approximately 3 months	

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	10.3 (± 3.8)			
End of treatment	10.1 (± 4.3)			
Change from baseline	-0.2 (± 3.4)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in mean cardiac index from baseline to EOT.

End point title	Change in mean cardiac index from baseline to EOT.
-----------------	--

End point description:

Right heart catheterization was performed for cardiac hemodynamic assessment at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: L/min/m ²				
arithmetic mean (standard deviation)				
Baseline	3.34 (± 0.71)			
End of treatment	3.38 (± 0.81)			
Change from baseline	0.04 (± 0.5)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in 6-minute walk distance (6MWD) from baseline to EOT.

End point title	Change in 6-minute walk distance (6MWD) from baseline to EOT.
-----------------	---

End point description:

The 6MWD was assessed at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT. The 6-minute walk test is a non-encouraged test that measures the distance walked for the duration of 6 min.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: meter				
arithmetic mean (standard deviation)				
Baseline	498.1 (± 86)			
End of treatment	492.8 (± 81.6)			
Change from baseline	-5.3 (± 29.1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Borg dyspnea score from baseline to EOT.

End point title	Change in Borg dyspnea score from baseline to EOT.
-----------------	--

End point description:

The Borg dyspnea score was assessed at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT. The Borg scale is a category-ratio scale, commonly used to evaluate the effects of exercise on dyspnea. The original and modified scales have ratio properties ranging from 0 = nothing at all to 10 = very, very severe, with descriptors from 0 to 10. Descriptors have been modified by others so that 10 has been labelled "extremely severe," or "the worst possible dyspnea imaginable."

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	4 (± 2.1)			
End of treatment	3.3 (± 2.1)			
Change from baseline	-0.7 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of participants with Improved, No Change, or Worsening of New York Heart Association Functional Class (NYHA FC) from baseline to EOT.

End point title	Number of participants with Improved, No Change, or Worsening of New York Heart Association Functional Class (NYHA FC) from baseline to EOT.
-----------------	--

End point description:

NYHA FC was assessed at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT. Disease severity was assessed by NYHA classification of pulmonary arterial hypertension criteria: Class I: no limitation of physical activity (PA). Ordinary PA: no undue dyspnea/fatigue, chest pain, near syncope. Class II: slight limitation of PA. Comfortable at rest. Ordinary PA: undue dyspnea/fatigue, chest pain, near syncope. Class III: marked limitation of PA. Comfortable at rest. Less than ordinary PA:

undue dyspnea/fatigue, chest pain, near syncope. Class IV: inability to carry out PA without symptoms. Right heart failure. Dyspnea/fatigue may even have been present at rest. Discomfort increased by any PA.

End point type	Other pre-specified
End point timeframe:	
Approximately 3 months	

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: participants				
Improved	1			
No change	35			
Worsened	4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in N-terminal pro-B-type natriuretic peptide (NT proBNP) from baseline to EOT.

End point title	Change in N-terminal pro-B-type natriuretic peptide (NT proBNP) from baseline to EOT.
End point description:	
Blood sampling for NT proBNP was performed at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT.	
End point type	Other pre-specified
End point timeframe:	
Approximately 3 months	

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: ng/L				
arithmetic mean (standard deviation)				
Baseline	599.97 (± 1164.21)			
End of treatment	613.56 (± 1155.9)			
Change from baseline	13.58 (± 318.58)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Effectiveness Score of the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) from Baseline to EOT.

End point title	Change in Effectiveness Score of the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) from Baseline to EOT.
-----------------	---

End point description:

Patients were required to complete the TSQM-9 questionnaire at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT. The TSQM-9 is a validated instrument to assess patients' satisfaction with medication, including a three question effectiveness scale. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
median (confidence interval 95%)				
Baseline	77.78 (74.07 to 83.33)			
End of treatment	77.78 (72.22 to 83.33)			
Change from baseline	0 (-5.56 to 0)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Convenience Score of the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) from Baseline to EOT.

End point title	Change in Convenience Score of the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) from Baseline to EOT.
-----------------	---

End point description:

Patients were required to complete the TSQM-9 questionnaire at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT. The TSQM-9 is a validated instrument to assess patients'

satisfaction with medication, including a three question convenience scale. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

End point type	Other pre-specified
End point timeframe:	
Approximately 3 months	

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
median (confidence interval 95%)				
Baseline	52.78 (44.44 to 61.11)			
End of treatment	66.67 (55.56 to 72.22)			
Change from Baseline	16.67 (5.56 to 22.22)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Global Satisfaction Score of the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) from Baseline to EOT.

End point title	Change in Global Satisfaction Score of the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) from Baseline to EOT.
-----------------	---

End point description:

Patients were required to complete the TSQM-9 questionnaire at Screening or Day 1, prior to switch from Flolan® to EFI/ACT-385781A and at EOT. The TSQM-9 is a validated instrument to assess patients' satisfaction with medication, including a three question global satisfaction scale. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

End point type	Other pre-specified
End point timeframe:	
Approximately 3 months	

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: units on a scale				
median (confidence interval 95%)				

Baseline	72.92 (61.11 to 84.72)			
End of treatment	76.39 (68.06 to 84.72)			
Change from baseline	2.08 (0 to 8.33)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of participants with adverse events leading to discontinuation of study drug from baseline to EOT.

End point title	Number of participants with adverse events leading to discontinuation of study drug from baseline to EOT.
-----------------	---

End point description:

Adverse events that led to discontinuation of study drug from the start of study treatment until the end of study treatment were recorded.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Approximately 3 months

End point values	Epoprostenol for injection (EFI/ACT-385781A)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) that occurred from the start of study treatment until 24 h after the end of study treatment were recorded. In addition, all serious AEs that occurred up to 30 days after the end of study treatment were also recorded.

Adverse event reporting additional description:

All treated set

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14
--------------------	----

Reporting groups

Reporting group title	EFI/ACT-385781A
-----------------------	-----------------

Reporting group description:

EFI/ACT-385781A administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.

Serious adverse events	EFI/ACT-385781A		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 41 (17.07%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device connection issue			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device damage			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device dislocation			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection	Additional description: pseudomonas		
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	EFI/ACT-385781A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 41 (78.05%)		
Vascular disorders			
FLUSHING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Cardiac disorders			
PALPITATIONS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Nervous system disorders			
HEADACHE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	12 / 41 (29.27%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			

DYSпноEA subjects affected / exposed occurrences (all) EPISTAXIS alternative dictionary used: MedDRA 14 subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3 3 / 41 (7.32%) 3		
Musculoskeletal and connective tissue disorders PAIN IN JAW subjects affected / exposed occurrences (all) PAIN IN EXTREMITY alternative dictionary used: MedDRA 14 subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 6 3 / 41 (7.32%) 3		
Infections and infestations NASOPHARYNGITIS alternative dictionary used: MedDRA 14 subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2010	<p>1. A modification to the formulation of the study drug and resulting changes to its stability, availability and its name were described:</p> <ul style="list-style-type: none">– Changes in study drug excipients were described. In contrast to the previous formulation (EFI1), this new formulation (EFI2) has not been approved by FDA.– Instructions for study drug packaging, and preparation, handling and storage of the study drug solution were updated accordingly.– The drug name was changed to Epoprostenol for injection (EFI).– An additional dose strength of 0.5 mg was added. <p>2. The numbers of participating countries and of patients to be enrolled were increased from 20 to 25–35 patients.</p> <p>3. Changes were made in the core patient information and informed consent form.</p> <p>4. Some editorial changes were made for clarification and to correct typing errors.</p> <p>5. The authors of the protocol and the sponsor's contact details and signatories were changed.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported