



## Clinical trial results:

### An open-label extension of study AC-066A301 investigating the safety and tolerability of ACT-385781A in patients with pulmonary arterial hypertension (PAH)

#### Summary

EudraCT number	2010-018320-10
Trial protocol	BE NL ES IT
Global end of trial date	15 June 2015

#### Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

#### Trial information

##### Trial identification

Sponsor protocol code	AC-066A302
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01470144
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	ACTELION Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Thomas Pfister, ACTELION Pharmaceuticals Ltd, medinfo_ch@actelion.com
Scientific contact	Thomas Pfister, ACTELION Pharmaceuticals Ltd, medinfo_ch@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 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2015
Global end of trial reached?	Yes
Global end of trial date	15 June 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess safety and tolerability of Epoprostenol for injection in patients with PAH

Protection of trial subjects:

Prior to the start of the AC-066A302 study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB). Actelion ensured that each IEC/IRB consulted was adequately constituted to provide assurance of that protection.

The protocol and any written material provided to the subject were reviewed and approved by the appropriate IEC or IRB before the study was started. Amendments to the protocol were also reviewed by the appropriate IEC/IRB before their implementation.

The investigator ensured that study AC-066A302 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.

Documentary evidence of adequate Good Clinical Practice (GCP) training of the investigator was collected. GCP training was provided to investigators, if required. A written commitment to comply with GCP and the study protocol was obtained from the investigator.

The study enrolled patients who had completed AC-066A301 and had not obtained access to commercially available and reimbursed EFI2 at the time of ending participation in AC-066A301. Patients participating in AC-066A301 were male or female and  $\geq 18$  years of age with PAH who had been treated with Flolan® for at least 12 months and were on a stable dose for at least 3 months prior to enrollment in AC-066A301. The patient population was consistent with the indication approved for Flolan®. Additional eligibility criteria at enrollment into AC-066A301 were intended to reduce variability due to disease characteristics and co-morbidities. Eligible patients were required to have completed study AC-066A301. Patients for whom continued treatment with EFI2 was no longer considered appropriate were not eligible.

Background therapy:

Concomitant PAH medications were allowed, except any prostacyclin or prostacyclin analog other than EFI2. Any other concomitant investigational drugs were forbidden.

Evidence for comparator: -

Actual start date of recruitment	15 June 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	France: 20
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 8

Worldwide total number of subjects	41
EEA total number of subjects	33

Notes:

<b>Subjects enrolled per age group</b>	
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:

Extension study for patients who completed EPITOME-2 (AC-066A301). Patients continued to receive EFI (epoprostenol sodium). In 6 countries (FR, CA, BE, NL, IT, ES) at 8 expert centers for the treatment of patients with pulmonary arterial hypertension. Recruitment started on 15 June 2011 and was completed on 02 February 2012.

### Pre-assignment

Screening details:

None

### Period 1

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

### Arms

<b>Arm title</b>	Treatment
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Arm description:

All patients who received at least one dose of EFI2

Arm type	Experimental
Investigational medicinal product name	epoprostenol sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous drip use

Dosage and administration details:

EFI2 was supplied in 10-mL glass vials that contained 0.5 or 1.5 mg epoprostenol sodium as a lyophilized powder. EFI2 was reconstituted and further diluted with either sterile water for injection or 0.9% w/v sodium chloride for injection, to obtain the "ready -to-use solution" for injection. This solution was administered by continuous i.v. infusion via a central venous catheter using an ambulatory infusion pump. Infusion sets with an in-line 0.22 micron filter were used. During long-term infusion, the dose of EFI2 was to be adjusted under medical supervision according to therapeutic need and tolerability.

Number of subjects in period 1	Treatment
Started	41
Completed	31
Not completed	10
Adverse event, serious fatal	1
Adverse event, non-fatal	2
Patient's and investigator's decision	1
Lung transplant	6



## Baseline characteristics

### Reporting groups

Reporting group title	Treatment
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Reporting group description:

All patients who received at least one dose of EFI2

Reporting group values	Treatment	Total	
Number of subjects	41	41	
Age categorical			
Units: Subjects			
Adults (18-64 years)	38	38	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	44.8		
standard deviation	± 13.9	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	30	30	
Male	11	11	

### Subject analysis sets

Subject analysis set title	All treated set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The All treated set consists of all patients who received at least one dose of study drug in study AC-066A302 and is identical to the All treated set reported for AC-066A301.

Reporting group values	All treated set		
Number of subjects	41		
Age categorical			
Units: Subjects			
Adults (18-64 years)	38		
From 65-84 years	3		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	44.8		
standard deviation	± 13.9		
Gender categorical			
Gender categorical description			
Units: Subjects			

Female	30		
Male	11		


## End points

### End points reporting groups

Reporting group title	Treatment
Reporting group description: All patients who received at least one dose of EFI2	
Subject analysis set title	All treated set
Subject analysis set type	Safety analysis
Subject analysis set description: The All treated set consists of all patients who received at least one dose of study drug in study AC-066A302 and is identical to the All treated set reported for AC-066A301.	

### Primary: Not applicable

End point title	Not applicable <sup>[1]</sup>
End point description: No primary endpoint was defined. This was an exploratory safety study.	
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 was performed.	

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: Not applicable				

Notes:

[2] - not applicable

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Treatment-emergent adverse events

End point title	Treatment-emergent adverse events
End point description:	
End point type	Other pre-specified
End point timeframe: Up to 24 hours post treatment	



End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Number of patients	41			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Exposure duration

End point title	Exposure duration
End point description:	
Duration of exposure to EFI	
End point type	Other pre-specified
End point timeframe:	
Study start to end of treatment	

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: year				
median (full range (min-max))	2.44 (0.5 to 4)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From study start to end of treatment plus 1 day.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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### Reporting groups

Reporting group title	Treatment
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Reporting group description:

Reporting group 1 description

Serious adverse events	Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 41 (85.37%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Investigations			
Transplant evaluation			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain natriuretic peptide increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Road traffic accident			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Lung transplant			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Medical device change			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 1		
Angina pectoris			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac flutter			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Coronary artery stenosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus arrhythmia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dizziness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
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 dislocation			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Device occlusion			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Device alarm 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	2 / 41 (4.88%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Catheter site pain				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device breakage				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device connection issue				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion site vesicles				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				

Device leakage			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic pseudocyst			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary arterial hypertension			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
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			
Catheter site infection			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Device related infection	Additional description: Not local infection, not sepsis		
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Bronchitis moraxella			
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 cellulitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia primary atypical			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
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 %

<b>Non-serious adverse events</b>	Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 41 (95.12%)		
Investigations			
Weight decreased			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	8		

Nervous system disorders			
	Headache		
	subjects affected / exposed	12 / 41 (29.27%)	
	occurrences (all)	15	
	Dizziness		
	subjects affected / exposed	3 / 41 (7.32%)	
	occurrences (all)	3	
General disorders and administration site conditions			
	Fatigue		
	subjects affected / exposed	8 / 41 (19.51%)	
	occurrences (all)	8	
	Oedema peripheral		
	subjects affected / exposed	4 / 41 (9.76%)	
	occurrences (all)	5	
	Pyrexia		
	subjects affected / exposed	4 / 41 (9.76%)	
	occurrences (all)	4	
	Asthenia		
	subjects affected / exposed	3 / 41 (7.32%)	
	occurrences (all)	3	
Gastrointestinal disorders			
	Diarrhoea		
	subjects affected / exposed	10 / 41 (24.39%)	
	occurrences (all)	14	
	Nausea		
	subjects affected / exposed	7 / 41 (17.07%)	
	occurrences (all)	8	
	Abdominal distension		
	subjects affected / exposed	4 / 41 (9.76%)	
	occurrences (all)	4	
	Vomiting		
	subjects affected / exposed	5 / 41 (12.20%)	
	occurrences (all)	6	
	Dyspepsia		
	subjects affected / exposed	3 / 41 (7.32%)	
	occurrences (all)	4	



Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	10		
Cough			
subjects affected / exposed	10 / 41 (24.39%)		
occurrences (all)	10		
Epistaxis			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	7		
Oropharyngeal pain			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Pulmonary arterial hypertension			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	6		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	10 / 41 (24.39%)		
occurrences (all)	10		
Pain in jaw			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	6		
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Bronchitis subjects affected / exposed occurrences (all)  Gastroenteritis subjects affected / exposed occurrences (all)  Catheter site infection subjects affected / exposed occurrences (all)  Sinusitis subjects affected / exposed occurrences (all)	10 / 41 (24.39%) 14  8 / 41 (19.51%) 14  4 / 41 (9.76%) 5  4 / 41 (9.76%) 6  3 / 41 (7.32%) 3		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)  Decreased appetite subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 11  3 / 41 (7.32%) 3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2010	<ol style="list-style-type: none"><li>1. A modification to the formulation of the study drug and resulting changes to its stability, availability and its name were described:<ul style="list-style-type: none"><li>– Changes in study drug excipients were described.</li><li>– Instructions for study drug packaging, and preparation, handling and storage of the study drug solution were updated accordingly.</li><li>– The drug name was changed to Epoprostenol for injection (EFI).</li><li>– An additional dose strength of 0.5 mg was added.</li></ul></li><li>2. The estimated treatment duration (until commercialization of the new formulation) was updated from 4–16 months to 2 years.</li><li>3. An increase in the numbers of participating countries and of patients to be enrolled was described, in line with changes made in study AC-066A301.</li><li>4. Changes were made in the core patient information and informed consent form.</li><li>5. Some editorial changes were made for clarification and to correct typographical errors.</li><li>6. The authors of the protocol and the sponsor's contact details and signatories were changed.</li></ol>
15 June 2011	<ol style="list-style-type: none"><li>1. The instructions for the handling and storage of the study drug solution were updated, based on data from an additional in-use stability study that showed that the diluted EFI solution could be stored and administered for longer periods of time than previously described.</li><li>2. An increase in the number of patients to be enrolled from 25-30 to 40 patients was described, in line with changes made in study AC-066A301.</li><li>3. Changes were made in the core patient information and informed consent form.</li><li>4. Some editorial changes were made for clarification and to correct typographical errors.</li><li>5. The authors of the protocol and the sponsor's contact details and signatories were changed.</li></ol>
28 February 2012	<ol style="list-style-type: none"><li>1. The instructions for storage and handling of study drug solution were adjusted for consistency with the proposed Summary of Product Characteristics for EFI.</li><li>2. Following withdrawal of sitaxentan from the market by its license holder, inclusion criteria and allowed concomitant medications were updated to exclude sitaxentan.</li><li>3. The use of an infusion set with an in-line filter was specified in Section 3.3.1 of the protocol, consistent with the proposed Summary of Product Characteristics for EFI. Prior to this Amendment, the use of an in-line filter had been indicated in the list of ancillary supplies (protocol section 3.6.2) only.</li><li>4. The planned study duration was revised, with a delay in enrollment anticipated for AC-066A301 and hence AC-066A302.</li><li>5. Changes were made in the core patient information and informed consent form.</li><li>6. Minor clarifications, including administrative changes and corrections of typographical errors, were made.</li></ol>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24439982>