Clinical trial results:
A multicenter, open-label, single-sequence, cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag

Summary

EudraCT number	2016-004035-21
Trial protocol	DE
Global end of trial date	29 May 2018

Results information

Result version number	v1 (current)
This version publication date	03 May 2019
First version publication date	03 May 2019

Trial information

Trial identification

Sponsor protocol code	AC-065A309

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03187678
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical trial disclosure deck, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.com
Scientific contact	Clinical trial disclosure deck, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.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	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2018
Global end of trial reached?	Yes
Global end of trial date	29 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess whether it was safe for patients with PAH to temporarily change from selexipag tablets (Uptravi®) to selexipag given intravenously, and then switching back to the initial oral dose of selexipag.

Protection of trial subjects:

The study was designed and conducted in compliance with International Good clinical Practice (ICH-GCP) Guidelines, the ethical principles of the Declaration of Helsinki and with the laws and regulations of the countries in which the study was conducted.

Background therapy:

PAH-specific therapies (i.e., ERA, PDE-5 inhibitor, or sGC stimulator) were allowed if subjects were on a stable dose. Uptravi was a mandatory background therapy for participation in this study. Uptravi was to be prescribed as part of the subjects standard therapy and had to be temporarily interrupted during intravenous (iv) selexipag administration.

Evidence for comparator: -

Actual start date of recruitment	04 December 2017
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	Germany: 13
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	20
EEA total number of subjects	13

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)	15
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Twenty-two patients treated with Uptravi for pulmonary arterial hypertension (PAH) were screened. Twenty of them were enrolled in the study.

Period 1

Period 1 title	Period 1 (oral selexipag)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Selexipag

Arm description:

Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.

Arm type	Experimental
Investigational medicinal product name	Oral selexipag (Uptravi®)
Investigational medicinal product code	ACT-293987
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Uptravi was used as an auxiliary medicinal product, as part of the PAH standard treatment and according to the local prescribing information.

Number of subjects in period 1	Selexipag
Started	20
Completed	20

Period 2

Period 2 title	Period 2 (intravenous selexipag)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Selexipag

Arm description:

Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.

Arm type	Experimental
Investigational medicinal product name	Intravenous selexipag
Investigational medicinal product code	ACT-293987
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The intravenous dose was individualized for each subject to correspond to his/her current oral dose of Uptravi® and infused over 87 min.

Number of subjects in period 2	Selexipag
Started	20
Completed	20

Period 3

Period 3 title	Period 3 (oral selexipag)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Selexipag

Arm description:

Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.

Arm type	Experimental
Investigational medicinal product name	Oral selexipag (Uptravi®)
Investigational medicinal product code	ACT-293987
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Uptravi was used as an auxiliary medicinal product, as part of the PAH standard treatment and according to the local prescribing information.

Number of subjects in period 3	Selexipag
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Selexipag
Reporting group description:	
Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.	

Reporting group values	Selexipag	Total	
Number of subjects	20	20	
Title for AgeCategorical			
Units: subjects			
Adults (18-64 years)	15	15	
From 65 to 84 years	5	5	
85 years and over	0	0	
Title for AgeContinuous			
Units: years			
arithmetic mean	56.5		
standard deviation	± 9.43	-	
Title for Gender			
Units: subjects			
Female	16	16	
Male	4	4	
Race			
Units: Subjects			
Asian	1	1	
Black or African American	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or other Pacific Islander	0	0	
White	19	19	
Other	0	0	
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	
Non Hispanic or Latino	20	20	
World Health Organization Functional classes (WHO FC)			
Only subjects with WHO FC I, II or III at screening and baseline visits could be enrolled			
Units: Subjects			
FC I	1	1	
FC II	13	13	
FC III	6	6	
PAH-specific therapies at baseline			
The following PAH-specific therapies were allowed on top of Uptravi at baseline: endothelin receptor antagonists (ERA), phosphodiesterase type-5 (PDE-5) inhibitors and soluble guanylate cyclase (sGC) stimulators.			
Units: Subjects			
PDE-5 inhibitors	1	1	

sGC stimulator	1	1	
ERA + sGC stimulator	5	5	
ERA + PDE-5 inhibitor	13	13	
PAH etiology at baseline			
Patients with the following types of pulmonary arterial hypertension (PAH) could be enrolled: idiopathic PAH, heritable PAH, PAH associated with another disease or condition, including connective tissue disease (CTD), congenital heart disease (CHD), HIV infection, portal hypertension, schistosomiasis.			
Units: Subjects			
Idiopathic PAH	13	13	
Heritable PAH	1	1	
Drug or toxin induced PAH	0	0	
Associated with CTD	4	4	
Associated with CHD	1	1	
Associated with HIV	0	0	
Associated with portal hypertension	1	1	
Associated with schistosomiasis	0	0	
Uptravi dose at screening Units: Subjects			
200 ug twice daily	0	0	
400 ug twice daily	1	1	
600 ug twice daily	2	2	
800 ug twice daily	2	2	
1000 ug twice daily	3	3	
1200 ug twice daily	2	2	
1400 ug twice daily	1	1	
1600 ug twice daily	9	9	

End points

End points reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.

Reporting group title	Selexipag

Reporting group description:

Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.

Reporting group title	Selexipag

Reporting group description:

Subjects treated with a stable dose of oral selexipag (Uptravi) between 200 and 1600 ug twice daily continued to take Uptravi at their prescribed dose during Period 1 (Day 1), then they were switched to intravenous (iv) selexipag during period 2 (3 doses, Day 2 & Day 3) and back to Uptravi during Period 3.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All enrolled subjects who received at least one dose of Uptravi or intravenous selexipag during any of the study periods

Subject analysis set title	iv safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All enrolled subjects who received at least one dose of intravenous selexipag during period 2

Primary: Number of participants with at least one adverse event (AE)

End point title	Number of participants with at least one adverse event (AE)[1]

End point description:

AE is any untoward medical event that occurs in a participant during the course of the study whether or not considered by the investigator as related to the study treatment.

End point type	Primary

End point timeframe:

From Day 1 to Day 37

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: No formal statistic analyses were performed on these safety data

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	15			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with prostacyclin-associated adverse events

End point title	Number of participants with prostacyclin-associated adverse events[2]

End point description:

Prostacyclin-associated AE include headache, diarrhea, nausea, vomiting, jaw pain, myalgia, pain in the extremity, flushing and arthralgia.

End point type	Primary

End point timeframe:

From Day 1 to Day 37

Notes:

[2] - 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: No formal statistic analyses were performed on these safety data.

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	7			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with adverse event related to injection site reactions

End point title	Number of participants with adverse event related to injection site reactions[3]

End point description:

This is the number of participants with at least one clinically significant reaction at the injection site (e.g., erythema/redness, tenderness, swelling, induration, hemorrhage at the injection site) occurring on the days of intravenous (iv) selexipag injection.

End point type	Primary

End point timeframe:

Day 2 and Day 3

Notes:

[3] - 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: No formal statistic analyses were performed on these safety data.

End point values	iv safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with prostacyclin-associated AEs leading to study treatment discontinuation

End point title	Number of participants with prostacyclin-associated AEs leading to study treatment discontinuation[4]

End point description:

This is the number of subjects who discontinued the i.v. selexipag treatment due to prostacyclin-associated adverse events (headache, diarrhea, nausea, vomiting, jaw pain, myalgia, pain in the extremity, flushing and arthralgia).

End point type	Primary

End point timeframe:

Day 2 and Day 3

Notes:

[4] - 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: No formal statistic analyses were performed on these safety data.

End point values	iv safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with PAH-related adverse events

End point title	Number of participants with PAH-related adverse events[5]

End point description:

This is the number of participants with at least one AE considered to be related to pulmonary arterial hypertension during the course of the study.

End point type	Primary

End point timeframe:

From Day 1 to Day 37

Notes:

[5] - 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: No formal statistic analyses were performed on these safety data.

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 2 to Day 37

Adverse event reporting additional description:

Treatment-emergent AEs are reported, i.e. serious and non-serious AEs starting on or after the first iv infusion of selexipag, which is the investigational treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Safety analysis set

Reporting group description:

All enrolled subjects who received at least one dose of Uptravi or intravenous selexipag during any of the study periods

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Right Ventricular Failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Rhegmatogenous Retinal Detachment			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blindness Unilateral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 20 (65.00%)		
Injury, poisoning and procedural complications			
Incorrect Drug Administration Rate			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vascular Access Complication			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	9		
Tension Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			

Infusion Site Erythema subjects affected / exposed occurrences (all) Infusion Site Swelling subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3 1 / 20 (5.00%) 1 2 / 20 (10.00%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 2 1 / 20 (5.00%) 3 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Renal and urinary disorders			

Chromaturia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Pain in Jaw subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported