Clinical trial results:
A multi-centre, multinational, open-label study to evaluate the long-term safety, tolerability and efficacy of selexipag / ACT 293987 (NS-304) in the treatment of pulmonary arterial hypertension in subjects aged 18 years and over (open-extension study to NS 304/-02)

Summary

EudraCT number	2007-006453-12
Trial protocol	HU AT FR BE GB IT DE
Global end of trial date	19 December 2017

Results information

Result version number	v1 (current)
This version publication date	30 December 2018
First version publication date	30 December 2018

Trial information

Trial identification

Sponsor protocol code	NS-304/-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 Desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.com
Scientific contact	Clinical Trial Disclosure Desk, 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	20 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2017
Global end of trial reached?	Yes
Global end of trial date	19 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to collect and evaluate long-term safety and tolerability data of selexipag treatment in subjects with pulmonary arterial hypertension (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, and with the ethical principles laid down in the Declaration of Helsinki

Background therapy:

Oral anticoagulants, calcium channel blockers, diuretics, cardiac glyocsides, supplement oxygen, endothelin receptor antagonists, phosphodiesterase inhibitors and riociguat were allowed.

Evidence for comparator: -

Actual start date of recruitment	09 October 2008
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	Austria: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 7
Worldwide total number of subjects	39
EEA total number of subjects	39

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

39 subjects (31 previously randomized to selexipag and 8 previously randomized to placebo in the previous NS-304/-02 study) were enrolled into the open-label extension study NS-304/-03, from 7 sites in 7 countries.

Pre-assignment

Screening details:

Only the subjects who had completed Visit 7 (Week 17) of the preceding double-blind study NS-304/-02 and who signed the informed consent form to take part in the open-label extension study were eligible to be enrolled in NS-304/-03.

Period 1

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

Arms

Arm title	Selexipag

Arm description:

Subjects who received selexipag during NS-304/-02 continued with their maximal tolerated dose of selexipag. Subjects who received placebo during NS-304/-02 started with 200 µg selexipag b.i.d. from Day 1 to Day 3, then the dose was up-titrated in 200 µg b.i.d. increments up to the maximum tolerated dose (MTD) for each subject but not above 800 µg during the titration phase. Thereafter these subjects continued with their individual maximal tolerated dose. After Week 24, the dose could be adjusted (not exceeding 1600 µg following Amendment 5).

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	ACT-293987, NS-304
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily administration (b.i.d.) with an interval of approximately 12 hours

Number of subjects in period 1	Selexipag
Started	39
Completed	7
Not completed	32
Consent withdrawn by subject	1
Disease progression	13
Adverse events	6
Death	10
Treatment goal not reached	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Selexipag
Reporting group description:	
Subjects who received selexipag during NS-304/-02 continued with their maximal tolerated dose of selexipag. Subjects who received placebo during NS-304/-02 started with 200 µg selexipag b.i.d. from Day 1 to Day 3, then the dose was up-titrated in 200 µg b.i.d. increments up to the maximum tolerated dose (MTD) for each subject but not above 800 µg during the titration phase. Thereafter these subjects continued with their individual maximal tolerated dose. After Week 24, the dose could be adjusted (not exceeding 1600 µg following Amendment 5).	

Reporting group values	Selexipag	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
Age continuous			
Age at baseline is the age reported when subjects were enrolled in the NS-304/-02 study.			
Units: years			
median	54		
full range (min-max)	19 to 80	-	
Gender categorical Units:			
Male	5	5	
Female	34	34	
Ethnicity Units: Subjects			
Caucasian	36	36	
Asian	2	2	
Other	1	1	
PAH etiology			
PAH etiology at baseline is the PAH etiology reported when subjects were enrolled in the NS-304/-02 study			
Units: Subjects			
Idiopathic PAH	28	28	
Familial PAH	2	2	
PAH associated with CTD	5	5	
PAH associated with corrected CHD	2	2	
PAH associated with anorexigen use	2	2	
WHO Functional class (FC)			
WHO FC for each subject in the open-label extension study was collected on Day 1 of study NS-304/-03, before starting the open-label treatment.			
Units: Subjects			
WHO FC I	3	3	
WHO FC II	17	17	
WHO FC III	19	19	
PAH-specific concomitant therapy			
PAH-specific concomitant therapy means PAH-specific therapies reported as ongoing on Day 1 of study NS-304/-03, before starting the open-label treatment.			
Units: Subjects			

Endothelin receptor antagonist (ERA)	13	13	
Phosphodiesterase-5 inhibitor (PDE5i)	12	12	
ERA + PDE5i	14	14	
Time since PAH diagnosis			
This is the time since pulmonary arterial hypertension diagnosis at Day 1 of study NS-304/-03, before starting the open-label treatment.			
Units: Days			
median	1071		
full range (min-max)	251 to 10062	-	

End points

End points reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects who received selexipag during NS-304/-02 continued with their maximal tolerated dose of selexipag. Subjects who received placebo during NS-304/-02 started with 200 µg selexipag b.i.d. from Day 1 to Day 3, then the dose was up-titrated in 200 µg b.i.d. increments up to the maximum tolerated dose (MTD) for each subject but not above 800 µg during the titration phase. Thereafter these subjects continued with their individual maximal tolerated dose. After Week 24, the dose could be adjusted (not exceeding 1600 µg following Amendment 5).

Primary: Number of subjects with any treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with any treatment-emergent adverse events (TEAEs)[1]

End point description:

A treatment emergent adverse event (TEAE) was defined as any AE with an onset on the first day of selexipag intake in NS-304/-03 up to 3 days after treatment discontinuation (EOT + 3 days), whether or not considered related to the study treatment.

End point type	Primary

End point timeframe:

From Day 1 to EOT + 3 days

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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects	38			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with TEAEs of mild, moderate or severe intensity

End point title	Number of subjects with TEAEs of mild, moderate or severe intensity[2]

End point description:

Treatment-emergent adverse events (TEAEs) were classified into three intensity categories: mild AE (usually transient and do not interfere with the subject daily's activities), moderate AE (low level of inconvenience to the subject and may interfere with daily's activities), severe AE (interruption of the subject's usual daily activities).
The number of subjects with at least one adverse event of mild, moderate or severe intensity was reported.

End point type	Primary

End point timeframe:

from Day 1 to EOT + 3 days

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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
Mild intensity	33			
Moderate intensity	37			
Severe intensity	27			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with TEAEs causally related to the study treatment

End point title	Number of subjects with TEAEs causally related to the study treatment[3]

End point description:

The causal relationship between the study treatment (selexipag) and the adverse event (TEAE) was characterized as unrelated (no reasonable possibility that the study treatment caused the AE), unlikely (only a remote connection exists between the study treatment and the AE; other conditions appear to explain the AE), possible (the association of the AE with the study treatment is unknown; however the AE is not reasonably supported by other conditions) or probable (a reasonable temporal sequence of the AE with the study treatment administration exists).
The number of subjects with at least one TEAE characterized as "possible" or "probable" by the investigator was reported as causally related to the study treatment.

End point type	Primary

End point timeframe:

From day 1 to EOT + 3 days

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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects	28			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with fatal treatment-emergent adverse events

End point title	Number of subjects with fatal treatment-emergent adverse events[4]

End point description:

The number of subjects with at least one treatment-emergent adverse event leading to death was reported

End point type	Primary

End point timeframe:

From Day 1 to EOT + 3 days

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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with adverse events leading to study treatment discontinuation

End point title	Number of subjects with adverse events leading to study treatment discontinuation[5]

End point description:

Subjects with at least one AE leading to permanent withdrawal of the study treatment (selexipag) were reported

End point type	Primary

End point timeframe:

From day 1 up to treatment discontinuation

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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects	18			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment-emergent adverse events of special interest (AESI)

End point title	Number of subjects with treatment-emergent adverse events of special interest (AESI)[6]

End point description:

AESI were defined based on the selexipag European Risk Management Plan (EU RMP) and included the following: Hypotension, Anemia / decrease in hemoglobin concentration, Hyperthyroidism, Major adverse cardiac event (MACE), Acute renal failure and renal impairment, Bleeding events, Light-dependent non-melanoma skin tumors, Ophthalmological effects associated with retinal vascular system, Gastrointestinal disturbances denoting intestinal intussusception.

End point type	Primary

End point timeframe:

From Day 1 to EOT + 3 days

Notes:

[6] - 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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
Hypotension	5			
Anemia, decrease in hemoglobin	8			
MACE	8			
Acute renal failure and renal impairment	3			
Bleeding events	11			
Overall (any categories)	23			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of marked laboratory tests abnormalities

End point title	Incidence of marked laboratory tests abnormalities[7]

End point description:

The number of subjects enrolled in NS-304/-03 with marked abnormalities in hematology or chemistry variables were to be reported. Marked abnormality was considered for subjects who presented an abnormality post-baseline which was not present at baseline.

End point type	Primary

End point timeframe:

From Day 1 to Week 24

Notes:

[7] - 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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
Hemoglobin decrease (<100 g/L)	2			
Creatinine increase (> 1.5 x ULN)	1			
Sodium increase (>150 mmol/L)	1			
Potassium increase (> 5.5 mmol/L)	2			
Potassium decrease (< 3 mmol/L)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of marked abnormalities in vital signs

End point title	Incidence of marked abnormalities in vital signs[8]

End point description:

The number of subjects enrolled in NS-304/-03 with marked abnormalities in systolic / diastolic blood pressure (SBP/DBP) or pulse rate were to be reported. Marked abnormality was considered for subjects who presented an abnormality post-baseline which was not present at baseline.

End point type	Primary

End point timeframe:

From Day 1 up to the last study visit

Notes:

[8] - 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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
SBP < 90 mmHg	6			
SBP decrease > 40 mmHg from Baseline	1			
DBP < 50 mmHg	1			
DBP decrease > 20 mmHg from baseline	5			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of QTcF abnormalities

End point title	Incidence of QTcF abnormalities[9]

End point description:

The number of subjects enrolled in NS-304/-03 with QTcF abnormalities as assessed by ECG were to be reported. Marked abnormality was considered for subjects who presented a QTcF prolongation post-baseline which was not present at baseline.

End point type	Primary

End point timeframe:

From Day 1 to Week 24

Notes:

[9] - 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 statistical analyses were planned for this study. Only descriptive analyses were performed for all variables.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Subjects				
QTcF > 450 ms	21			
QTcF > 480 ms	5			
QTcF > 500 ms	2			
QTcF increase from baseline > 30 ms	5			
QTcF increase from baseline > 60 ms	1			
QTcF > 450 ms and increase from baseline > 30 ms	4			
QTcF > 450 ms and increase from baseline > 60 ms	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 6-minute walk distance over time

End point title	Change from baseline in 6-minute walk distance over time

End point description:

Walk distance is measured during the 6-minute walk test (6MWT). 6MWT is a non-encouraged test, which measures the distance (in meters) covered by the subject during a 6-minute walk in a flat corridor. Change from baseline in 6MWT was analyzed at various timepoints during the study. Thirty-nine subjects had a 6MWT measure available at baseline. If the number of subjects included in the analysis for a specific timepoint was less than 10 this timepoint was not reported here.

End point type	Secondary

End point timeframe:

From Day 1 to the last study visit

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: meters				
median (full range (min-max))				
Week 12 (N=34)	1.0 (-100 to 125)			
Week 24 (N=34)	-0.5 (-172 to 115)			

Month 12 (N=30)	-15.0 (-195 to 167)			
Month 18 (N=29)	-10.0 (-233 to 147)			
Month 24 (N=26)	-19.5 (-256 to 185)			
Month 30 (N=25)	-27 (-208 to 114)			
Month 36 (N=23)	-45 (-121 to 178)			
Month 42 (N=21)	-30 (-247 to 247)			
Month 48 (N=19)	-27 (-228 to 330)			
Month 54 (N=18)	-34.5 (-150 to 270)			
Month 60 (N=18)	-20.5 (-342 to 355)			
Month 66 (N=16)	-31 (-172 to 371)			
Month 72 (N=15)	-50 (-256 to 370)			
Month 78 (N=15)	-29 (-268 to 357)			
Month 84 (N=10)	-20.5 (-114 to 359)			
Month 90 (N=11)	-25 (-96 to 373)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 to EOT + 3 days for non-serious and serious AEs and up to EOT + 30 days for deaths (all causes)	
Adverse event reporting additional description:	
Day 1 is the first day of enrollment in the open-label phase (NS-304/-03)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Selexipag
Reporting group description:	
A total of 39 subjects received selexipag during NS-304/-03 for a median duration of 1712 days (range: 11-3347 days), with 20 and 8 subjects receiving selexipag for a cumulative duration of at least 48 months and 96 months, respectively.	

Serious adverse events	Selexipag		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 39 (74.36%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign gastrointestinal neoplasm			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myelodysplastic syndrome			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Balloon atrial septostomy			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac ablation			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cranioplasty			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung transplant			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mastectomy			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transurethral prostatectomy			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal			

conditions			
Pregnancy			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Euthanasia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oedema peripheral			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			
subjects affected / exposed	12 / 39 (30.77%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 1		
Pulmonary hypertension			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental disorder			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Catheterisation cardiac			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications				
Alcohol poisoning				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute right ventricular failure				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Atrial flutter				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac arrest				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			

Cardiac failure			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Palpitations			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Right ventricular failure			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 2		
Tachycardia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Hypochromic anaemia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic congestion			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pain of skin			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 39 (2.56%)		
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	Selexipag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 39 (97.44%)		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Hot flush			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Chest pain			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	10		
Fatigue			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	7		
Malaise			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	11 / 39 (28.21%)		
occurrences (all)	14		
Pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Pyrexia			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Haemoptysis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Pulmonary arterial hypertension			
subjects affected / exposed	12 / 39 (30.77%)		
occurrences (all)	13		
Respiratory disorder			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Sleep apnoea syndrome			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Throat irritation			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Blood uric acid increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	4		

Ligament sprain subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all) Right ventricular failure subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 5 / 39 (12.82%) 7 2 / 39 (5.13%) 2 2 / 39 (5.13%) 2 5 / 39 (12.82%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	 8 / 39 (20.51%) 11 19 / 39 (48.72%) 31 2 / 39 (5.13%) 2 7 / 39 (17.95%) 10		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 6 / 39 (15.38%) 7		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2		

Vertigo				
subjects affected / exposed	8 / 39 (20.51%)			
occurrences (all)	9			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	3 / 39 (7.69%)			
occurrences (all)	4			
Abdominal pain upper				
subjects affected / exposed	4 / 39 (10.26%)			
occurrences (all)	4			
Constipation				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	3			
Diarrhoea				
subjects affected / exposed	17 / 39 (43.59%)			
occurrences (all)	18			
Dry mouth				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	2			
Gastritis				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	2			
Gastrooesophageal reflux disease				
subjects affected / exposed	4 / 39 (10.26%)			
occurrences (all)	5			
Nausea				
subjects affected / exposed	9 / 39 (23.08%)			
occurrences (all)	10			
Vomiting				

subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1 3 / 39 (7.69%) 4		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2 2 / 39 (5.13%) 2		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 3 / 39 (7.69%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Bursitis subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2 4 / 39 (10.26%) 6 2 / 39 (5.13%) 3 2 / 39 (5.13%) 2 3 / 39 (7.69%) 3		

Myalgia			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Osteoporosis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	11		
Pain in jaw			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	7		
Polyarthritis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	22		
Conjunctivitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		
Influenza			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Pneumonia			

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	16		
Rhinitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Viral upper respiratory tract infection			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	21		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2008	Main reasons for amendment: Operation and sponsorship of the study was changed from Nippon Shinyaku Ltd to Actelion Pharmaceuticals Ltd; Study drug number NS-304 changed to ACT-293987
25 November 2008	Main reasons for amendment: Because the results of an in vitro phototoxicity study suggested that selexipag and its active metabolite have phototoxic potential, this information was added as well as information on the precautions to be taken regarding sun exposure. A new inclusion criteria was introduced to include only subjects who were willing and able to refrain from sunbathing, prolonged exposure to sun and artificial sunlight (such as solarium), or UV-A/UV-B treatment, and to limit skin and eye exposure to sunlight by taking appropriate precautions (protective clothing, sunscreen, and sunglasses) from the first dose until 14 days after study treatment discontinuation.
10 February 2009	Main reasons for amendment: Study duration was extended from the existing 24 weeks until the earliest of one of the following: approval of marketing authorization for selexipag in PAH, decision by Actelion Pharmaceuticals Ltd to stop the study, or decision by the subject or investigator to discontinue study treatment.
25 June 2009	Main reasons for amendment: Activities previously managed by the CRO (Quintiles) were taken over by Actelion Pharmaceuticals Ltd
03 November 2010	Main reasons for amendment: -In accordance with the other ongoing studies (AC-065A302 and AC-065A303), the maximum dose of selexipag allowed in the present study was increased from 800 µg b.i.d. to 1600 µg b.i.d.; -change in the manufacturer of the selexipag tablets from Nippon Shinyaku Ltd to Excella Pharma GmbH - addition of new phase 1 study results.
17 June 2012	Main reasons for amendment: -A phase 1 clinical trial studying the phototoxicity of selexipag did not indicate a clinically relevant phototoxic potential of selexipag at doses of 800 and 1200 µg b.i.d. after UV-A and UV-B irradiation in healthy male subjects. Therefore, a footnote was added to the inclusion criterion on sun exposure to indicate that no extra precautions were necessary regarding sun exposure; - New findings from toxicologic studies in animals were added (retinal toxicity, nonmalignant neoplastic changes in the thyroid) -Change in selexipag packager and packaging.
16 January 2014	Main reasons for amendment: - ACT-293987 replaced by Selexipag in the protocol; - new findings from non clinical studies were added (effects on platelet aggregation in vitro; effects liver drug metabolizin enzymes and thyroid hormones in mice) as well as update on Phase 1 and Phase 2 studies. - Addition of an exclusion criteria: Females who were breast-feeding, pregnant or planned to become pregnant during the study and females who were not using a highly effective method of birth control with a failure rate of less than 1% per year, were to be excluded - Specification on how to manage subjects with liver impairment (based on the results of a Phase 1 study): If, during the course of the study, a subject developed or progressed to Child-Pugh B liver impairment, it was the responsibility of the investigator to assess the benefit-risk of maintaining the subject on study treatment; if a subject developed or progressed to Child Pugh C liver impairment, study treatment was to be discontinued. - Time to aggravation of PAH was added as a tertiary efficacy endpoint.

10 April 2015	Main reasons for amendment: -The condition that the site should inform the sponsor before a subject's dose was up titrated to a maximum of 1600 µg b.i.d. after Visit 5 was removed. However, it was clarified that the assessment/decision to up titrate was to be made only after a site visit (scheduled/unscheduled) was performed; -In order to avoid any treatment interruption if there was a lag period between the time when marketing authorization was granted and the time when selexipag could be commercially available to the subjects, the duration of NS-304/-03 study was set up to commercial availability of selexipag in the subject's country; - A new discontinuation criterion was introduced for subjects who were diagnosed with PVOD; - The concomitant use of selexipag and i.v., s.c., or inhaled prostacyclin and prostacyclin analogs was allowed temporarily when deemed medically justified; - The process of temporarily switching a subject from oral selexipag to another IP receptor with a more convenient route of administration with regard to the subjects medical condition and subsequently restarting selexipag was included in the protocol; -Riociguat was added as an allowed concomitant PAH medication: - because hyperthyroidism has been observed with selexipag and other IP receptor agonists, thyroid function tests were to be performed locally for individual subjects if deemed clinically indicated by the investigator.
24 January 2017	Main reasons for amendment: - Concomitant administration of strong CYP2C8 inhibitors such as gemfibrozil was to be avoided and selxipag dose adjustment could be required following concomitant administration of moderate CYP2C8 inducer such as rifampicin . These recommendations were added taking into account the results of a phase 1 study.
30 June 2017	Main reasons for amendment: - To include guidance for concomitant administration of selexipag and strong CYP2C8 inhibitors: concomitant administration of selexipag and strong CYP2C8 inhibitors such as gemfibrozil is prohibited until end-of-study in NS-304/-03. – To include information on other potential drug-drug interactions: The effect of moderate inhibitors of CYP2C8, and strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration may result in a significant increase in exposure to selexipag or its active metabolite.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported