Clinical trial results:
A Multi-center, Double-blind, Placebo-controlled, Phase 4 Study in Subjects with Pulmonary Arterial Hypertension to Assess the Effect of Selexipag on Daily Life Physical Activity and Subject's Self-reported Symptoms and their Impacts

Summary

EudraCT number	2017-000216-42
Trial protocol	GB IE SE DE AT PT FR
Global end of trial date	20 February 2020

Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021

Trial information

Trial identification

Sponsor protocol code	AC-065A404

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03078907
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Keilaranta 16, 02150 Espoo, Finland,
Public contact	Clinical Registry group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@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	23 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2020
Global end of trial reached?	Yes
Global end of trial date	20 February 2020
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 evaluate the effect of selexipag on daily life physical activity (DLPA) of subjects with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety assessment was based on reported adverse events, clinical laboratory tests (such as hematology clinical chemistry, N-terminal pro b-type natriuretic peptide (NT-pro BNP), blood samples for circulating biomarkers, thyroid function test [as hyperthyroidism has been observed with selexipag]), vital sign measurements, and pregnancy tests (for women of childbearing potential).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 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	Austria: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United Kingdom: 66
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	108
EEA total number of subjects	27

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)	85
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 108 subjects were randomized out of which 96 subjects completed the study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Selexipag

Arm description:

Subjects received Selexipag which was up-titrated from Day 1 (Week 1) to Week 12 to the individualized highest tolerated dose (HTD) which ranged from 200 microgram (mcg) to 1600 mcg twice daily (BID) orally. The dose was increased in increments of 200 mcg BID, usually at weekly intervals, depending on the dose tolerability. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Selexipag was administered as tablets of 200 mcg in doses of up to 1600 mcg (8 tablets) orally twice daily.

Arm title	Placebo

Arm description:

Subjects received one to 8 tablets of 200 (mcg) matching placebo, administered up to a maximum dose up-titrated to 1600 mcg orally twice daily. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as matching tablets of 200 mcg in doses of up to 1600 mcg (8 tablets) orally twice daily.

Number of subjects in period 1	Selexipag	Placebo
Started	53	55
Completed	50	54
Not completed	3	1
Adverse Event	2	-
Subject decision	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Selexipag

Reporting group description:

Subjects received Selexipag which was up-titrated from Day 1 (Week 1) to Week 12 to the individualized highest tolerated dose (HTD) which ranged from 200 microgram (mcg) to 1600 mcg twice daily (BID) orally. The dose was increased in increments of 200 mcg BID, usually at weekly intervals, depending on the dose tolerability. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Reporting group title	Placebo

Reporting group description:

Subjects received one to 8 tablets of 200 (mcg) matching placebo, administered up to a maximum dose up-titrated to 1600 mcg orally twice daily. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Reporting group values	Selexipag	Placebo	Total
Number of subjects	53	55	108
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	43	85
From 65 to 84 years	11	12	23
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	49	49.8	
standard deviation	± 14.75	± 13.63	-
Title for Gender Units: subjects			
Female	35	42	77
Male	18	13	31

End points

End points reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects received Selexipag which was up-titrated from Day 1 (Week 1) to Week 12 to the individualized highest tolerated dose (HTD) which ranged from 200 microgram (mcg) to 1600 mcg twice daily (BID) orally. The dose was increased in increments of 200 mcg BID, usually at weekly intervals, depending on the dose tolerability. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Reporting group title	Placebo

Reporting group description:

Subjects received one to 8 tablets of 200 (mcg) matching placebo, administered up to a maximum dose up-titrated to 1600 mcg orally twice daily. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Primary: Change from Baseline to Week 24 in Actigraphy Assessed Daily Life Physical Activity (DLPA) for Variables Expressed in Minutes

End point title	Change from Baseline to Week 24 in Actigraphy Assessed Daily Life Physical Activity (DLPA) for Variables Expressed in Minutes

End point description:

Change from baseline to Week 24 of the DLPA activity parameters for daily time spent in non-sedentary activity (NSA) (as defined by Freedson ’98 and Koster ‘16) and daily time spent in moderate-to-vigorous physical activity (MVPA) as defined by Freedson ‘98 were reported. These variables were assessed by actigraphy and were expressed in minutes. Freedson 1998 established ranges of activity counts obtained from a hip worn accelerometer corresponding to commonly employed MET categories. Based on this work, threshold between sedentary and NSA was defined. This threshold is often referred to as Freedson’s 1998 publication. Koster 2016 defined the threshold between sedentary and NSA based on wrist-worn accelerometers on non-dominant hand, respectively. Positive change from baseline means improvement. The Full Analysis Set (FAS) included all subjects randomly assigned to a study treatment.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: minutes				
arithmetic mean (standard deviation)				
Daily time spent in NSA (Freedson ‘98)	-15.2 (± 79.78)	-25.2 (± 72.47)		
Daily time spent in MVPA (Freedson '98)	0.2 (± 34.48)	-1.9 (± 34.26)		
Daily time spent in NSA (Koster'16)	-0.7 (± 72.50)	-15.0 (± 62.27)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Daily time spent in non-sedentary activity (minutes), Freedson ‘98	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Least Square (LS) mean
Point estimate	13.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.366
upper limit	40.944
Variability estimate	Standard error of the mean
Dispersion value	13.695

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Daily time spent in MVPA (minutes), Freedson ‘98	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	LS mean
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.782
upper limit	15.396
Variability estimate	Standard error of the mean
Dispersion value	6.601

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Daily time spent in non-sedentary activity (minutes), Koster ‘16	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	LS mean
Point estimate	17.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.003
upper limit	41.619
Variability estimate	Standard error of the mean
Dispersion value	12.008

Primary: Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Percentage (%)

End point title	Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Percentage (%)

End point description:

Change from baseline to Week 24 of the DLPA activity parameters for daily time spent in non-sedentary activity (NSA) (Freedson '98), daily time spent in moderate-to-vigorous physical activity (MVPA) (Freedson '98) and dailytime spent in NSA (Koster '16) were reported. These variables were assessed by actigraphy andwere expressed in percentage (%). Freedson 1998 established ranges of activity counts obtained from a hip worn accelerometer corresponding to commonly employed MET categories. Based on this work, threshold between sedentary and NSA was defined. This threshold is often referred to as Freedson's 1998 publication. Koster 2016 defined the threshold between sedentary and NSA based on wrist-worn accelerometers on non-dominant hand, respectively. Positive change from baseline means improvement. The FAS included all subjects randomly assigned to a study treatment.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: Percentage				
arithmetic mean (standard deviation)				
Daily time spent in NSA (%), Freedson '98	0.08 (± 7.265)	-0.10 (± 6.439)		
Daily time spent in MVPA (%), Freedson '98	0.23 (± 3.342)	0.32 (± 3.513)		
Daily time spent in NSA (%), Koster '16	0.80 (± 7.158)	0.00 (± 6.269)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Percentage of daily time spent in non-sedentary activity (%), Freedson '98

Comparison groups	Selexipag v Placebo

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.713
upper limit	3.06
Variability estimate	Standard error of the mean
Dispersion value	1.204

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Percentage of daily time spent in MVPA (%), Freedson ‘98	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	LS mean
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.351
upper limit	1.258
Variability estimate	Standard error of the mean
Dispersion value	0.658

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Percentage of daily time spent in non-sedentary activity (%), Koster ‘16	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	LS mean
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.104
upper limit	3.618

Variability estimate	Standard error of the mean
Dispersion value	1.191

Primary: Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Counts per Minute (Counts/Minute)

End point title	Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Counts per Minute (Counts/Minute)

End point description:

Change from baseline to Week 24 of the DLPA activity parameter for volume of total daily activities and volume of NSA (Koster '16) were reported. These variables were assessed by actigraphy and were expressed in counts/minutes. Koster 2016 defined the threshold between sedentary and NSA based on wrist-worn accelerometers on non-dominant hand, respectively. Positive change from baseline means improvement. The FAS included all subjects randomly assigned to a study treatment.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: counts/minute				
arithmetic mean (standard deviation)				
Volume of total daily activities	29.3 (± 337.18)	18.8 (± 342.77)		
Volume of NSA, Koster '16	36.1 (± 342.11)	16.8 (± 351.08)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Volume of total daily activities (counts / minute)

Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	20.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-105.632
upper limit	146.958
Variability estimate	Standard error of the mean
Dispersion value	63.695

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Volume of non-sedentary activity (counts/minute), Koster '16	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	LS mean
Point estimate	27.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-101.945
upper limit	156.976
Variability estimate	Standard error of the mean
Dispersion value	65.291

Primary: Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Counts

End point title	Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Counts
End point description: Change from baseline to Week 24 of the DLPA activity parameters for volume of non-sedentary activity (Koster '16)were reported. These variables were assessed by actigraphy and were expressed in counts. Koster 2016 defined the threshold between sedentary and NSA based on wrist-worn accelerometers on non-dominant hand, respectively. Positive change from baseline means improvement. The FAS included all subjects randomly assigned to a study treatment.	
End point type	Primary
End point timeframe: Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)	

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: counts				
arithmetic mean (standard deviation)	3898 (± 345872)	-49187 (± 343402.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Selexipag v Placebo

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	58409
Confidence interval	
level	95 %
sides	2-sided
lower limit	-70444
upper limit	187263
Variability estimate	Standard error of the mean
Dispersion value	64985

Primary: Change from Baseline to Week 24 in Actigraphy DLPA for Variable Expressed in Step Counts

End point title	Change from Baseline to Week 24 in Actigraphy DLPA for Variable Expressed in Step Counts

End point description:

Change from baseline to Week 24 of the DLPA activity parameters for number of steps during awake time were reported. These variables were assessed by actigraphy and were expressed in step counts. Positive change from baseline means improvement. The Full Analysis Set (FAS) included all subjects randomly assigned to a study treatment.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: step counts				
arithmetic mean (standard deviation)	-32.4 (± 1288.64)	-170.9 (± 1076.87)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	201.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-242.977
upper limit	646.163
Variability estimate	Standard error of the mean
Dispersion value	224.212

Primary: Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Step Counts/Minute

End point title	Change from Baseline to Week 24 in Actigraphy DLPA for Variables Expressed in Step Counts/Minute

End point description:

Change from baseline to Week 24 of the DLPA activity parameters for number of steps during awake time were reported. These variables were assessed by actigraphy and were expressed in step counts/minute. Positive change from baseline means improvement. The Full Analysis Set (FAS) included all subjects randomly assigned to a study treatment.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: step counts/minute				
arithmetic mean (standard deviation)	0 (± 1.25)	0.0 (± 1.04)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.366
upper limit	0.51
Variability estimate	Standard error of the mean
Dispersion value	0.221

Primary: Change from Baseline to Week 24 in Total Sleep Time (TST)

End point title	Change from Baseline to Week 24 in Total Sleep Time (TST)[1]

End point description:

TST (in minutes) was assessed by actigraphy. Mean value from the last 14 days period on study treatment was evaluated and mean change from baseline was calculated. The FAS included all subjects randomly assigned to a study treatment. Data was not reported because the sleep episodes were not identified due to unexpected inaccuracy in automated sleep detection algorithm which resulted in missing/unreliable sleep data which would mislead the design of future trials and the interpretation of sleep results.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

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 inferential statistical hypothesis testing was planned for this endpoint.

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: minutes				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - Data was not reported for reason stated above.

[3] - Data was not reported for reason stated above.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline to Week 24 in Wake After Sleep Onset (WASO)

End point title	Change from Baseline to Week 24 in Wake After Sleep Onset (WASO)[4]

End point description:

WASO (in minutes) was assessed by actigraphy. Mean value from the last 14 days period on study treatment was evaluated and mean change from baseline was calculated. The FAS included all participants randomly assigned to a study treatment. Data was not reported because the sleep episodes were not identified due to unexpected inaccuracy in automated sleep detection algorithm which resulted in missing/unreliable sleep data which would mislead the design of future trials and the interpretation of sleep results.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

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 inferential statistical hypothesis testing was planned for this endpoint.

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: minutes				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Data was not reported for reason stated above.

[6] - Data was not reported for reason stated above.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline to Week 24 in Number of Awakenings

End point title	Change from Baseline to Week 24 in Number of Awakenings[7]

End point description:

Number of awakenings was assessed by actigraphy. Mean value from the last 14 days period on study treatment was evaluated and mean change from baseline was calculated. The FAS included all subjects randomly assigned to a study treatment. Data was not reported because the sleep episodes were not identified due to unexpected inaccuracy in automated sleep detection algorithm which resulted in missing/unreliable sleep data which would mislead the design of future trials and the interpretation of sleep results.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for 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 inferential statistical hypothesis testing was planned for this endpoint.

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: per night				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - Data was not reported for reason stated above.

[9] - Data was not reported for reason stated above.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline to Week 24 in Sleep Efficiency (SE)

End point title	Change from Baseline to Week 24 in Sleep Efficiency (SE)[10]

End point description:

SE (in percentage) was assessed by actigraphy. Mean value from the last 14 days period on study treatment was evaluated and mean change from baseline was calculated. The FAS included all subjects randomly assigned to a study treatment. Data was not reported because the sleep episodes were not identified due to unexpected inaccuracy in automated sleep detection algorithm which resulted in missing/unreliable sleep data which would mislead the design of future trials and the interpretation of sleep results.

End point type	Primary

End point timeframe:

Baseline and Week 24 (data collection was done during 14-Days each for Baseline and for Week 24)

Notes:

[10] - 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 inferential statistical hypothesis testing was planned for this endpoint.

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: percentage per night				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - Data was not reported for reason stated above.

[12] - Data was not reported for reason stated above.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Score

End point title	Change from Baseline to Week 24 in Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Score

End point description:

The PAH-SYMPACT has two main parts: symptoms (cardiopulmonary and cardiovascular)and impact (physical impacts and cognitive/emotional). The symptom part is a questionnaire completed daily for 7 consecutive days and contains 11 items. The impact part has a 7-day recall period and is completed on the seventh day of the symptoms questionnaire data collection period. It contains 11 items pertaining to the impact of PAH. The average Cardiopulmonary Symptoms and cardiovascular symptoms domain scores are determined based on the daily scores of the 6 and 5 items, respectively, reported on a 5-point Likert scale (from 0 to 4). The score ranges from 0=best to 4=worst. Mean value on each of the 7-day period was calculated for each specific domain score and corresponding mean change from baseline was determined. The FAS included all subjects randomly assigned to a study treatment. Here, 'n' (number of subjects analyzed) signifies the number of subjects evaluable for a specified category.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cardiopulmonary symptom (n=44, 52)	-0.030 (± 0.4160)	-0.080 (± 0.2564)		
Cardiovascular symptom (n=44, 52)	0.010 (± 0.3522)	-0.045 (± 0.3029)		
Physical impact (n=40, 50)	-0.043 (± 0.5932)	-0.074 (± 0.5470)		
Cognitive/emotional impact (n=40, 50)	0.000 (± 0.5311)	-0.090 (± 0.5992)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Change from Baseline to Week 24 in World Health Organization Functional Class (WHO FC)

End point title	Number of Subjects with Change from Baseline to Week 24 in World Health Organization Functional Class (WHO FC)

End point description:

The WHO FC of pulmonary hypertension is a physical activity rating scale as follows: Class I (No limitation of physical activity); Class II (Slight limitation of physical activity); Class III (Marked limitation of physical activity); and Class IV (Inability to carry out any physical activity without symptoms). The change from baseline in WHO FC was classified into "Improved", "No change" and "Worsened" compared to baseline. Deterioration, No Change, and Improvement are based on shift of risk category (I, II, III, IV) from baseline in WHO Functional Class. The FAS included all subjects randomly assigned to a study treatment. Here 'N' (number of subjects analyzed) included all subjects who were with assessments at both baseline and post-baseline time point.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	54		
Units: subjects				
Deterioration	2	1		
No change	33	43		
Improvement	9	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in 6-Minute Walk Distance (6MWD)

End point title	Change from Baseline to Week 24 in 6-Minute Walk Distance (6MWD)

End point description:

The 6MWD was the total distance walked during 6 minutes. Mean change from baseline (distance walked at Week 24 minus distance walked at baseline) was reported. The Full Analysis Set (FAS) included all subjects randomly assigned to a study treatment. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: meters				
arithmetic mean (standard deviation)	18.3 (± 54.47)	9.8 (± 60.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Borg Dyspnea Score

End point title	Change from Baseline to Week 24 in Borg Dyspnea Score

End point description:

The Borg dyspneas score was a self-rating scale to evaluate the severity of dyspnea (from 0 "no shortness of breath at all" to 10 "very, very severe / maximal shortness of breath"). It was completed immediately after the 6-minute walk test at Week 24 and at baseline. Mean change from baseline in scoring was reported. The Full Analysis Set (FAS) included all subjects randomly assigned to a study treatment. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.25 (± 2.122)	0.37 (± 1.869)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in N-Terminal Pro B-type Natriuretic Peptide (NT-proBNP)

End point title	Change from Baseline to Week 24 in N-Terminal Pro B-type Natriuretic Peptide (NT-proBNP)

End point description:

Change from baseline to Week 24 in NT-pro BNP levels was reported. The negative change from baseline means improvement. The Full Analysis Set (FAS) included all subjects randomly assigned to a study treatment. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	53		
Units: nanogram per liter (ng/L)				
geometric mean (confidence interval 95%)	0.91 (0.768 to 1.073)	0.98 (0.828 to 1.149)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 28 weeks

Adverse event reporting additional description:

Safety Analysis Set included the subjects who were who were randomized and received at least 1 dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects received Selexipag which was up-titrated from Day 1 (Week 1) to Week 12 to the individualized highest tolerated dose (HTD) which ranged from 200 microgram (mcg) to 1600 mcg twice daily (BID) orally. The dose was increased in increments of 200 mcg BID, usually at weekly intervals, depending on the dose tolerability. Up-titration was followed by a stable maintenance treatment period at the highest tolerated dose, from Week 13 to Week 24.

Reporting group title	Placebo

Reporting group description:

Subjects received one to 8 tablets of 200 (mcg), administered in doses of up to 1600 mcg, matching placebo orally twice daily up-titrated for 24 weeks.

Serious adverse events	Selexipag	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 53 (5.66%)	6 / 55 (10.91%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial Flutter			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Thyroid Nodule Removal			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Glossitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Selexipag	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 53 (98.11%)	52 / 55 (94.55%)	
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 53 (9.43%)	6 / 55 (10.91%)	
occurrences (all)	7	6	
Hot Flush			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	
occurrences (all)	2	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 53 (13.21%)	7 / 55 (12.73%)	
occurrences (all)	8	8	
Headache			
subjects affected / exposed	41 / 53 (77.36%)	26 / 55 (47.27%)	
occurrences (all)	76	49	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 53 (9.43%)	4 / 55 (7.27%)	
occurrences (all)	5	4	
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 53 (3.77%)	7 / 55 (12.73%)	
occurrences (all)	2	9	
Oedema Peripheral			

subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	
occurrences (all)	1	5	
Abdominal Pain Upper			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	28 / 53 (52.83%)	23 / 55 (41.82%)	
occurrences (all)	37	36	
Dyspepsia			
subjects affected / exposed	6 / 53 (11.32%)	0 / 55 (0.00%)	
occurrences (all)	7	0	
Nausea			
subjects affected / exposed	22 / 53 (41.51%)	15 / 55 (27.27%)	
occurrences (all)	31	21	
Vomiting			
subjects affected / exposed	13 / 53 (24.53%)	4 / 55 (7.27%)	
occurrences (all)	22	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	
occurrences (all)	4	3	
Dyspnoea			
subjects affected / exposed	4 / 53 (7.55%)	6 / 55 (10.91%)	
occurrences (all)	4	6	
Epistaxis			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	
occurrences (all)	4	3	
Nasal Congestion			
subjects affected / exposed	5 / 53 (9.43%)	2 / 55 (3.64%)	
occurrences (all)	5	2	
Oropharyngeal Pain			

subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	
occurrences (all)	2	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	
occurrences (all)	4	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 53 (20.75%)	8 / 55 (14.55%)	
occurrences (all)	15	9	
Back Pain			
subjects affected / exposed	4 / 53 (7.55%)	6 / 55 (10.91%)	
occurrences (all)	4	6	
Myalgia			
subjects affected / exposed	6 / 53 (11.32%)	3 / 55 (5.45%)	
occurrences (all)	7	3	
Pain in Extremity			
subjects affected / exposed	11 / 53 (20.75%)	1 / 55 (1.82%)	
occurrences (all)	15	1	
Pain in Jaw			
subjects affected / exposed	20 / 53 (37.74%)	5 / 55 (9.09%)	
occurrences (all)	29	5	
Infections and infestations			
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	5 / 53 (9.43%)	14 / 55 (25.45%)	
occurrences (all)	6	16	
Respiratory Tract Infection			
subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	
occurrences (all)	1	4	
Tonsillitis			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
Upper Respiratory Tract Infection			

subjects affected / exposed	6 / 53 (11.32%)	6 / 55 (10.91%)	
occurrences (all)	7	6	
Urinary Tract Infection			
subjects affected / exposed	0 / 53 (0.00%)	4 / 55 (7.27%)	
occurrences (all)	0	5	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	4 / 53 (7.55%)	1 / 55 (1.82%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2018	The global amendment was considered substantial and included the following changes: a change to the dosing instructions for study drug (selexipag/placebo) based on a drug-drug interaction study for clopidogrel; the pulmonary function test could be performed in the presence or absence of bronchodilation, whereby the eligible subject population remained unchanged; and the list of assessments was modified without affecting the endpoint variables.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No hypothesis testing planned for this exploratory study. Sleep data not reported as sleep episodes not identified due to inaccuracy in algorithm resulting in unreliable data that would mislead design of future trials and interpretation of results.

Notes: