# 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<br>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<br>Units: years | | | |
| arithmetic mean | 49 | 49.8 | |
| standard deviation | ± 14.75 | ± 13.63 | - |
| Title for Gender<br>Units: subjects | | | |
| Female | 35 | 42 | 77 |
| Male | 18 | 13 | 31 |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | Selexipag |

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Statistical analysis description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 | | |

| 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: