



Clinical trial results:

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Group-sequential, Adaptive, Phase 3 Study With Open-label Extension Period to Assess the Efficacy and Safety of Selexipag as an add-on to Standard of Care Therapy in Subjects With Inoperable or Persistent/Recurrent After Surgical and/or Interventional Treatment Chronic Thromboembolic Pulmonary Hypertension

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2018-002823-41 |
| Trial protocol | DE GB CZ BE NL HU AT BG DK PT IT |
| Global end of trial date | 07 June 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 16 June 2023 |
| First version publication date | 16 June 2023 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-065B302 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03689244 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|----------------------------------------------------------------------------------------|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| 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 | 07 June 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 June 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the effect of selexipag on pulmonary vascular resistance (PVR) versus placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (that is, technically non-operable) and persistent/recurrent CTEPH after surgical pulmonary endarterectomy (PEA) and/or interventional balloon pulmonary angioplasty [BPA]) treatment at Week 20.

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 Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 23 January 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Argentina: 2 |
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Bulgaria: 4 |
| Country: Number of subjects enrolled | Brazil: 11 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | China: 2 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Denmark: 7 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Korea, Republic of: 9 |
| Country: Number of subjects enrolled | Mexico: 5 |
| Country: Number of subjects enrolled | Poland: 4 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Portugal: 6 |
| Country: Number of subjects enrolled | Russian Federation: 7 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | Thailand: 6 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | Taiwan: 2 |
| Country: Number of subjects enrolled | Ukraine: 1 |
| Country: Number of subjects enrolled | United States: 8 |
| Worldwide total number of subjects | 128 |
| EEA total number of subjects | 49 |

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) | 60 |
| From 65 to 84 years | 67 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 321 subjects were screened, of which 128 were randomly assigned and received study intervention.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Double Blind Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Double-blind Period: Placebo |

Arm description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) twice daily (BID) on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the individual maximum tolerated dose (iMTD) in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be once daily (QD).

| | |
|----------------------------------------|----------|
| 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:

Subjects were administered with single dose of placebo matching to selexipag 200 mcg tablet orally in the evening of day 1 and continued the same dose BID on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg placebo until reaching the individual iMTD in the range of 200 to 1600 mcg placebo BID or QD.

| | |
|------------------|--------------------------------|
| Arm title | Double-blind Period: Selexipag |
|------------------|--------------------------------|

Arm description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be QD.

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Selexipag |
| Investigational medicinal product code | |
| Other name | JNJ-67896049 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with single dose of selexipag 200 mcg tablet orally in the evening of day 1 and continued the same dose BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching the individual iMTD in the range of 200 to 1600 mcg BID or QD.

| Number of subjects in period 1 | Double-blind Period: Placebo | Double-blind Period: Selexipag |
|---------------------------------------|------------------------------|--------------------------------|
| Started | 64 | 64 |
| Completed | 9 | 6 |
| Not completed | 55 | 58 |
| Consent withdrawn by subject | 7 | 8 |
| Physician decision | 2 | 2 |
| Death | 1 | - |
| Unspecified | 1 | 1 |
| Sponsor decision | 44 | 47 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Open Label Period |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Open Label Period: Selexipag (Ex-Placebo) |

Arm description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 20.8 months).

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Selexipag |
| Investigational medicinal product code | |
| Other name | JNJ-67896049 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received single tablet of selexipag 200 mcg orally BID. For subjects with Child-Pugh B or who had taken concomitantly a moderate CYP2C8 inhibitor, the dosing frequency was QD.

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Arm title | Open Label Period: Selexipag (Ex-Selexipag) |
| <p>Arm description:</p> <p>All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 19.8 months).</p> | |
| Arm type | Experimental |
| Investigational medicinal product name | Selexipag |
| Investigational medicinal product code | |
| Other name | JNJ-67896049 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received single tablet of selexipag 200 mcg orally BID. For subjects with Child-Pugh B or who had taken concomitantly a moderate CYP2C8 inhibitor, the dosing frequency was QD.

| Number of subjects in period 2 | Open Label Period: Selexipag (Ex-Placebo) | Open Label Period: Selexipag (Ex-Selexipag) |
|---------------------------------------|-------------------------------------------|---------------------------------------------|
| Started | 9 | 6 |
| Completed | 0 | 0 |
| Not completed | 9 | 6 |
| Consent withdrawn by subject | 1 | - |
| Physician decision | 1 | - |
| Sponsor decision | 7 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Double-blind Period: Placebo |
|-----------------------|------------------------------|

Reporting group description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) twice daily (BID) on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the individual maximum tolerated dose (iMTD) in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be once daily (QD).

| | |
|-----------------------|--------------------------------|
| Reporting group title | Double-blind Period: Selexipag |
|-----------------------|--------------------------------|

Reporting group description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be QD.

| Reporting group values | Double-blind Period: Placebo | Double-blind Period: Selexipag | Total |
|---------------------------------------------|------------------------------|--------------------------------|-------|
| Number of subjects | 64 | 64 | 128 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 24 | 36 | 60 |
| From 65 to 84 years | 39 | 28 | 67 |
| 85 years and over | 1 | 0 | 1 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 64 | 62 | |
| standard deviation | ± 13.22 | ± 14.38 | - |
| Title for Gender Units: subjects | | | |
| Female | 47 | 46 | 93 |
| Male | 17 | 18 | 35 |

End points

End points reporting groups

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title | Double-blind Period: Placebo |
| Reporting group description: | |
| Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) twice daily (BID) on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the individual maximum tolerated dose (iMTD) in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be once daily (QD). | |
| Reporting group title | Double-blind Period: Selexipag |
| Reporting group description: | |
| Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be QD. | |
| Reporting group title | Open Label Period: Selexipag (Ex-Placebo) |
| Reporting group description: | |
| All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 20.8 months). | |
| Reporting group title | Open Label Period: Selexipag (Ex-Selexipag) |
| Reporting group description: | |
| All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 19.8 months). | |

Primary: Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 20

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title | Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 20 |
| End point description: | |
| Change from baseline in PVR at Week 20 was reported. PVR was assessed by right or right and left heart catheterization. Change from Baseline was measured as ratio of post-dose visit value to baseline value. Hemodynamic set (HES) included all assigned subjects in the hemodynamic cohort. Here, "Measure type (Least Squares Mean)" indicated "Geometric LS mean". | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (Day 1, pre-dose), within 2 to 5 hours post-dose on Week 20 | |

| End point values | Double-blind Period: Placebo | Double-blind Period: Selexipag | | |
|----------------------------------------------|---------------------------------|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 47 | | |
| Units: Ratio | | | | |
| least squares mean (confidence interval 95%) | 89.52 (81.78 to 97.99) | 85.15 (77.97 to 92.99) | | |

Statistical analyses

| Statistical analysis title | Selexipag Versus Placebo |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Statistical analysis description: | |
| Ratio of Geometric mean of Selexipag to Placebo was reported. | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Selexipag |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.412 |
| Method | ANCOVA |
| Parameter estimate | Ratio of geometric LS mean |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.07 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For DB period: from first DB dose up to EDBT (that is, up to 27.7 months) and for OL extension period: from first OL dose up to 30 days after the last OL dose (that is, up to 21.8 months)

Adverse event reporting additional description:

Safety Analysis Set (SAF) included all subjects who received at least one dose of study treatment.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Double-blind Period: Placebo |
|-----------------------|------------------------------|

Reporting group description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was QD.

| | |
|-----------------------|---------------------------------------------|
| Reporting group title | Open Label Period: Selexipag (Ex-Selexipag) |
|-----------------------|---------------------------------------------|

Reporting group description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 19.8 months).

| | |
|-----------------------|-------------------------------------------|
| Reporting group title | Open Label Period: Selexipag (Ex-Placebo) |
|-----------------------|-------------------------------------------|

Reporting group description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 20.8 months).

| | |
|-----------------------|--------------------------------|
| Reporting group title | Double-blind Period: Selexipag |
|-----------------------|--------------------------------|

Reporting group description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was QD.

| Serious adverse events | Double-blind Period: Placebo | Open Label Period: Selexipag (Ex- Selexipag) | Open Label Period: Selexipag (Ex- Placebo) |
|---------------------------------------------------------------------|---------------------------------|----------------------------------------------------|--------------------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 64 (25.00%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| number of deaths (all causes) | 2 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral Cancer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate Cancer | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Foot Fracture | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower Limb Fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural Haemorrhage | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular Tachycardia | | | |

| | | | |
|------------------------------------------------------|----------------|---------------|---------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right Ventricular Failure | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular Block Second Degree | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial Flutter | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Iron Deficiency Anaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Multiple Organ Dysfunction Syndrome | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter Site Haematoma | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|----------------|---------------|---------------|
| Gastrointestinal disorders | | | |
| Discoloured Vomit | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis Acute | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Hypertension | | | |

| | | | |
|-------------------------------------------------|----------------|---------------|---------------|
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Failure | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Covid-19 Pneumonia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Bacterial | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic Shock | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypervolaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Double-blind Period: Selexipag | | |
|---------------------------------------------------------------------|-----------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 64 (14.06%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral Cancer | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate Cancer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Foot Fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower Limb Fracture | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural Haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right Ventricular Failure | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrioventricular Block Second Degree | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|------------------------------------------------------|----------------|--|--|
| Atrial Flutter | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Iron Deficiency Anaemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Multiple Organ Dysfunction Syndrome | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Catheter Site Haematoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Discoloured Vomit | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatitis Acute | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary Hypertension | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory Failure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |

| | | | | |
|-------------------------------------------------|----------------|--|--|--|
| Bronchitis | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Covid-19 Pneumonia | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonia Bacterial | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic Shock | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tonsillitis | | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral Infection | | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypervolaemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| 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 | Double-blind Period: Placebo | Open Label Period: Selexipag (Ex- Selexipag) | Open Label Period: Selexipag (Ex- Placebo) |
|-------------------------------------------------------|---------------------------------|----------------------------------------------------|--------------------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 64 (70.31%) | 5 / 6 (83.33%) | 9 / 9 (100.00%) |
| Investigations | | | |
| Blood Glucose Increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Hot Flush | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flushing | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 1 / 6 (16.67%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 1 | 1 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------|----------------------|
| Dizziness subjects affected / exposed occurrences (all) | 7 / 64 (10.94%) 8 | 0 / 6 (0.00%) 0 | 2 / 9 (22.22%) 2 |
| Headache subjects affected / exposed occurrences (all) | 14 / 64 (21.88%) 24 | 2 / 6 (33.33%) 2 | 6 / 9 (66.67%) 11 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 6 (16.67%) 1 | 0 / 9 (0.00%) 0 |
| Blood and lymphatic system disorders Iron Deficiency Anaemia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 9 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | 0 / 6 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Chest Pain subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 6 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | 0 / 6 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Oedema subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 6 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Oedema Peripheral subjects affected / exposed occurrences (all) | 8 / 64 (12.50%) 11 | 0 / 6 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 9 (0.00%) 0 |
| Gastrointestinal disorders | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------|-----------------------|---------------------|---------------------|
| Irritable Bowel Syndrome subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 5 | 1 / 6 (16.67%) 1 | 3 / 9 (33.33%) 5 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 6 (16.67%) 1 | 3 / 9 (33.33%) 4 |
| Diarrhoea subjects affected / exposed occurrences (all) | 9 / 64 (14.06%) 11 | 1 / 6 (16.67%) 2 | 5 / 9 (55.56%) 8 |
| Abdominal Pain Upper subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 6 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Abdominal Distension subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Abdominal Discomfort subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 6 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 9 / 64 (14.06%) 10 | 0 / 6 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Pulmonary Hypertension subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 6 (16.67%) 1 | 0 / 9 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 6 (16.67%) 1 | 0 / 9 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 6 | 1 / 6 (16.67%) 1 | 3 / 9 (33.33%) 4 |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Back Pain | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | 0 / 6 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 6 | 0 | 1 |
| Flank Pain | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle Spasms | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | 0 / 6 (0.00%) | 4 / 9 (44.44%) |
| occurrences (all) | 5 | 0 | 6 |
| Pain in Extremity | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | 1 / 6 (16.67%) | 1 / 9 (11.11%) |
| occurrences (all) | 4 | 1 | 1 |
| Pain in Jaw | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 6 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 2 | 0 | 2 |
| Infections and infestations | | | |
| Covid-19 | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | 0 / 6 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 4 | 0 | 2 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 6 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 6 (16.67%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| Decreased Appetite | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 6 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Steroid Diabetes | | | |

| | | | |
|-----------------------------|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin D Deficiency | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 6 (16.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|-------------------------------------------------------|-----------------------------------|--|--|
| Non-serious adverse events | Double-blind Period: Selexipag | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 60 / 64 (93.75%) | | |
| Investigations | | | |
| Blood Glucose Increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences (all) | 6 | | |
| Hot Flush | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences (all) | 2 | | |
| Flushing | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | | |
| occurrences (all) | 5 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences (all) | 1 | | |
| Palpitations | | | |
| subjects affected / exposed | 6 / 64 (9.38%) | | |
| occurrences (all) | 10 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 64 (12.50%) | | |
| occurrences (all) | 9 | | |
| Headache | | | |
| subjects affected / exposed | 36 / 64 (56.25%) | | |
| occurrences (all) | 65 | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Hypoaesthesia subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |
| Blood and lymphatic system disorders Iron Deficiency Anaemia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 1 / 64 (1.56%) 1 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest Pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 4 2 / 64 (3.13%) 2 6 / 64 (9.38%) 11 0 / 64 (0.00%) 0 5 / 64 (7.81%) 5 5 / 64 (7.81%) 6 | | |
| Gastrointestinal disorders Irritable Bowel Syndrome subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 17 / 64 (26.56%) 29 | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| Vomiting subjects affected / exposed occurrences (all) | 11 / 64 (17.19%) 14 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 38 / 64 (59.38%) 57 | | |
| Abdominal Pain Upper subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 5 | | |
| Abdominal Distension subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | | |
| Abdominal Discomfort subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | | |
| Pulmonary Hypertension subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 3 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 14 / 64 (21.88%) 16 | | |
| Back Pain subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 5 | | |
| Flank Pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------|------------------------|--|--|
| Muscle Spasms subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 3 | | |
| Myalgia subjects affected / exposed occurrences (all) | 7 / 64 (10.94%) 7 | | |
| Pain in Extremity subjects affected / exposed occurrences (all) | 13 / 64 (20.31%) 16 | | |
| Pain in Jaw subjects affected / exposed occurrences (all) | 16 / 64 (25.00%) 20 | | |
| Infections and infestations Covid-19 subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 5 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | | |
| Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | | |
| Decreased Appetite subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 6 | | |
| Steroid Diabetes subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | | |
| Vitamin D Deficiency subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 09 January 2019 | <ul style="list-style-type: none">Several inclusion criteria were revised with the aim of ensuring the recruitment of subjects who could potentially benefit from medical therapy (only technically non operable participants assessed based on imaging review for all CTEPH subpopulations) and who had substantially impaired pulmonary vascular function (PVR greater than or equal to ≥ 400 dynes.second/centimeter⁵ or ≥ 5 Wood units).Statistical changes were made following interactions with health authorities. |
| 16 April 2020 | <ul style="list-style-type: none">The study design was revised to power the study for the additional clinical endpoint, time to clinical worsening (TTCW). As a result, elements of the study design, key secondary endpoints, sample size, testing hierarchy and analysis timepoints were amended to ensure the evaluation of 6-minute walk distance (6MWD) and TTCW endpoints.The DB period was changed from a fixed duration of 52 weeks to a variable duration (maximum 52 months) based on the timepoint at which the overall target number of TTCW events would be reached (or earlier following the recommendation of the independent data monitoring committee (IDMC) or sponsor's decision).The stratification factor of CTEPH population was redefined to inoperable (with or without BPA) versus persistent/recurrent after PEA (including PEA followed by BPA).For the non-hemodynamic cohort, the PVR threshold for inclusion was changed to ≥ 300 dyn.sec/cm⁵ or ≥ 3.75 Wood units.The sponsor's standardised guidelines for the assessments heart catheterisation (HC), 6MWT and Borg dyspnea index (BDI) were added to the protocol and the Borg CR10 Scale® was added.A clinical event committee (CEC) was set up in order to ensure independent adjudication of clinical worsening events. |
| 29 September 2020 | <ul style="list-style-type: none">Statistical changes were made in line with the resolution of food and drug administration (FDA) queries.The maximum duration of the DB period was increased from 52 months to 59 months.Safety reporting requirements were updated in line with Janssen processes. |

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.

Failure to meet success on the primary endpoint led to termination of the study for futility and thus the pre-planned testing hierarchy was no longer applicable, and all efficacy analyses other than the primary endpoint (PVR) were exploratory.

Notes: