Janssen Research & Development

Statistical Analysis Plan

Long-term single-arm open-label study, to assess the efficacy and tolerability of selexipag in participants with pulmonary arterial hypertension

Protocol AC-065A303/GRIPHON OL; Phase 3

ACT-293987 / JNJ 67896049 (selexipag)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	14Apr2021	Not Applicable	Initial release
2.0	23Sep2021	Wording update, added details on AEs and CMs outputs	Improve clarity, check consistency with DPS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical data analyses of the long-term single-arm open-label study AC-065A303/GRIPHON OL (A303) for the purpose of the Clinical Study Report (CSR).

All enrolled participants were rolled over from the preceding double-blind study AC-065A302/GRIPHON (A302) without any wash-out period. With respect to safety assessment for long-term use of selexipag, safety data for the selexipag treatment in A302 study (median exposure duration 18.8 months) cannot be disregarded. Therefore, the interim A303 data (cut-off date on the 01 September 2019) and A302 data were concatenated for the supplemental New Drug Application (sNDA) / Marketing Authorization Application (MAA) submissions for the long-term selexipag safety and survival in PAH as well as for update of the Risk Management Plan (RMP).

For the A303 CSR, the following two types of safety information will be provided:

- Safety information collected under the A303 study.
- Safety information collected during selexipag treatment under the A302 and/or A303 studies (Completed summary at the end of A303 study can be used to update the sNDA/MAA tables – selexipag treated set based on 01 September 2019 cut-off).

This SAP refers to the documents listed in Table 1.

Table 1: Key Reference Documents

Document	**Date, Version**
Study Protocol AC-065A303 (GRIPHON OL)	Final version 9 (D-19.045 / EDMS-RIM-264143)
CRF specifications (GRIPHON OL)	Final Version: 20 May 2010
CRF specifications (GRIPHON)	Final Version: 12 May 2010
SAP for labeling update – long term survival	Final version 2 (D-19.320 / EDMS-RIM-265325)
Summary of Clinical Safety – selexipag long-term treatment of Pulmonary Arterial Hypertension	Approved: 04 June 2020 (D-20.178 / EDMS-RIM-264693)

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM). Source data are those provided by Actelion Clinical Development Data Management (CDDM) via Statistical Programming And Computing Environment (SPACE) system. To prevent a violation of China's Human Genetic Resources (HGR) Regulation, data of participants in China for A303 that were due beyond 20 December 2019 are either not collected in clinical database or will be excluded from SDTM.

All descriptive or formal statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise specified.

For the Medical Dictionary for Regulatory Activities (MedDRA) version, it will NOT be updated to the latest available version at the time of database lock. The MedDRA version 22.0 will be used to be in line with the sNDA/MAA submissions for long-term safety and survival in PAH.

1.1. Objectives

The main objective of this study is to assess long-term safety and tolerability of selexipag in participants with PAH.

1.2. Study Design

This is a multicenter, open-label study to assess long-term safety and tolerability of selexipag in participants with PAH.

Participants (males or females aged 18 years or older) from the study A302 were enrolled between 07 July 2010 and 02 September 2014 in this A303 study. This participant population consists of 3 cohorts:

- Cohort 1: Participants who completed the study A302 including the Treatment Extension Period (TEP) as scheduled per protocol (i.e., treated until unblinding of the study) without morbidity event.
- Cohort 2: Participants who experienced a morbidity event (had to be confirmed by the Critical Event Committee [CEC]) during the study A302.
- Cohort 3: Participants who experienced a worsening of PAH during the TEP of A302 and for whom a written approval to enter study A303 had been obtained from the sponsor.

The study is conducted in 155 centers in 39 countries.

Visit 1 in the A303 study should correspond to the last visit in study A302. If this was not possible, Visit 1 had to be performed not later than 2 weeks (14 days) after the last visit in study A302.

Participants of Cohort 2 and Cohort 3 were enrolled in the A303 study without knowledge of their previous treatment to preserve the integrity of the double-blind A302 study. All these participants entered the titration period of A303, i.e., they started selexipag at the lowest dose (200 µg bid).

Participants of Cohort 1 were eligible to enter the A303 study with knowledge of their previous study intervention allocation (selexipag or placebo). Participants who were receiving selexipag in A302 directly entered the maintenance period in A303 at the same dose of selexipag they were receiving at the end of the A302 TEP, except participants who were with treatment interruption ≥ 3 days between studies would enter the titration period of A303. Participants who were receiving placebo in A302 entered first the titration period of A303, i.e., started selexipag at the lowest dose (200 µg bid). Participants with a treatment interruption of at least 3 days between both studies (irrespective of whether randomized to selexipag or placebo) also entered the titration period of A303.

Treatment in the titration period of A303 was started at a selexipag dose of 200 µg bid with subsequent up-titration by 200 µg bid increments to achieve the individual MTD (maximum

1600 µg bid) for administration during the maintenance period. Maintenance treatment was planned to continue until the earliest of (1) selexipag becoming commercially available in this indication in the participant's country, (2) the sponsor deciding to stop the A303 study, or (3) the participant or the investigator deciding to discontinue study intervention.

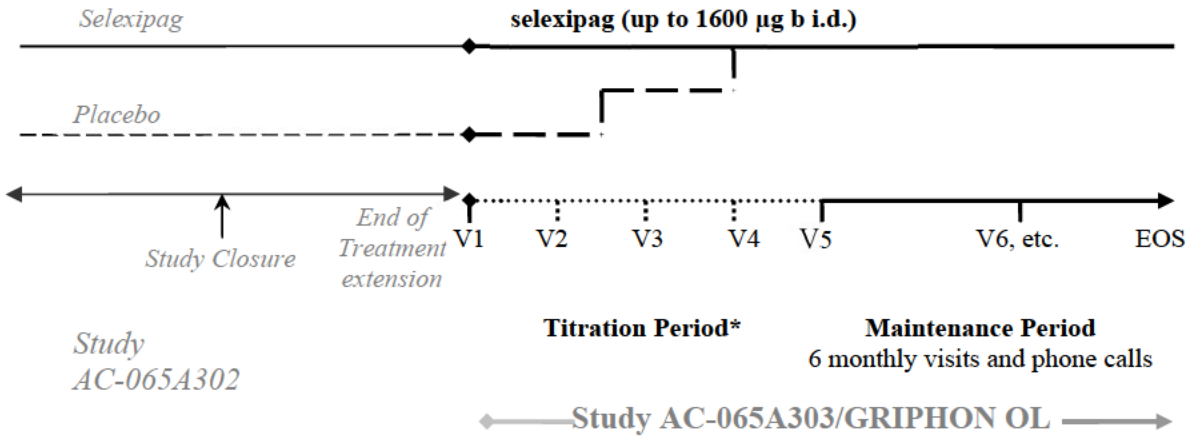
Each participant had his/her selexipag dose up-titrated up to his/her individual highest tolerated dose. Participants would receive new medication bottles at Visit 1, Visit 5 and every 6 months until the end of the A303 study. If a participant would enter the titration period, additional medication bottles would be given at Visit 2, 3, and 4.

At the end of the open-label study or after permanent discontinuation of study intervention, the end of study (EOS) visit will be performed and a post-treatment safety follow-up period will follow (30 days as recommended in the protocol; this is the last planned contact date).

The Data Monitoring Committee involved in the study A302 have reviewed safety data from A303 study up to 01 July 2016 (date of disbandment of the committee).

No interim analysis was planned in the protocol.

Figure 1: Study design



* Titration period only for participants with a morbidity event (confirmed by the CEC) or PAH worsening during TEP, participants on placebo in study AC-065A302, and participants with treatment interruption ≥ 3 days between studies

b.i.d. = twice daily, CEC = Critical Event Committee, EOS = End of Study, OL = Open Label, V= Visit

Titration period was applied to participants with a morbidity event or PAH worsening during TEP, participants on placebo in study AC 065A302 and participants with treatment interruption ≥ 3 days between studies (Figure 1 above). More information about Titration period can be found in Sections 5.5.1.1 and 5.5.2.3.

2. STATISTICAL HYPOTHESES

Not applicable.

3. SAMPLE SIZE DETERMINATION

Not applicable.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

In GRIPHON (A302) and GRIPHON OL (A303), two consecutive trials, a participant could go through one or more periods, which form a specific treatment sequence from A302 to A303 as summarized in Table 2. For each treatment sequence a participant is counted only once.

Table 2: Summary of Consecutive GRIPHON (A302) and GRIPHON OL (A303) Studies (Periods) and Treatment Sequence

Treatment sequence	Consecutive periods for ADaM datasets	
	Period 1	Period 2
	AC-065A302 (A302)	AC-065A303 (A303)
Selexipag / selexipag	Selexipag ←---------- analysis phase 1 ----------→ ←---------- analysis phase 2 ---------→ ←---------- analysis phase 3 ----------→	
Selexipag / not applicable	Selexipag ←---------- analysis phase 1 ----------→ ←---------- analysis phase 3 ----------→	Not entered in Period 2
Placebo / selexipag*	Placebo ←---------- analysis phase 1 ----------→	Selexipag ←---------- analysis phase 2 ----------→ ←---------- analysis phase 3 ----------→

*Participants who received Placebo in A302 and did not enter in A303 are not shown because they are not included in any analysis per this SAP.

To provide comprehensive long-term safety information, two analysis sets will be used and are defined as follows (Table 3):

Table 3: Description of Analysis Sets

Analysis Sets	Description
Treated Set – OL	The treated set - OL (OLS) includes all participants who received at least one dose of study intervention in the A303. This is a subset of the Selexipag-Treated Set defined below. Under this Analysis set, the following three groups will be summarized: - Ex-Selexipag: participants who received Selexipag in A302 - Ex-placebo: participants who received placebo in A302 - Total A303 This analysis set consists of data collected during "Analysis phase 2" in Table 2 (baseline (BL) is defined in Section 5.1.5.1)
Selexipag-treated Set (A302+A303)	The Selexipag-treated set (STS) includes all participants who received selexipag treatment at any time during A302 or A303. Under this Analysis set, the following two groups will be summarized:

Table 3: Description of Analysis Sets

Analysis Sets	Description
	- Selexipag in A302: Participants who received selexipag in A302 and did or did not enter A303. (This subset will be separately analyzed in Section 5.5.2.4.1). - All: Participants who received selexipag in A302 and/or A303 This analysis set consists of data collected during "Analysis phase 3" in Table 2 (BL is defined in Section 5.1.5.2)

The layout of summary tables will have both analysis sets and the respective groups displayed side by side (with "Total" column too), unless otherwise specified:

	Treated Set - OL (A303) ^			Selexipag -treated Set (A302 + A303)	
	Ex-Selexipag	Ex-placebo	Total A303	Selexipag in A302 §	All*
	330	379	709	574	953

A303= AC-065A303/GRIPHON OL, A302= AC-065A302/GRIPHON.
^Participants treated in A303.
§Participants who received selexipag in A302 and did or did not enter in A303.
*All participants who received selexipag in A302 and/or A303, i.e., selexipag start in A302 or in A303 (Ex-placebo)

The treatment group in the previous A302 study will be based on the "actual treatment group" (available in SDTM). A participant was randomized to placebo in A302 but received by mistake a single dose of selexipag on one occasion only. This participant was on placebo for more than 3 years before entering A303. This participant was assigned to selexipag in the safety analysis set of the A302 CSR (with cut-off in April 2014), and assigned to placebo in the safety analysis set of the A302 TEP-CSR (summarizing incremental information collected after the initial CSR cut-off up to end of treatment in A302). To avoid overestimation of selexipag treatment duration (especially in the mortality analyses), in this SAP this participant will be assigned to the placebo group in A302, and the selexipag initiation date will be the first selexipag treatment in A303. This revised approach has been applied to all safety summary (i.e., the PBRERs/DSURs, RMP, IB and summary of safety with long-term safety and survival for sNDA/MAA submission) except the initial NDA/MAA submission in 2014.

5. STATISTICAL ANALYSES

5.1. General Considerations

This is an open-label extension study. No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. No efficacy analysis is expected.

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits on A302 and A303. Table 4 lists the visit windows and the target days for planned visits. The reference day is Study Day 1 (Section 5.1.2). If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point. Listed below are the analysis visit windows and the target days for each visit defined in the protocol.

Table 4: Visit Windows

Parameter	Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Safety parameters	1	Baseline	No limit – to 1	1
	2	Week 4	2 to 42	28
	3	Week 8	43 to 84	56
	4	Week 16	85 to 147	112
	5	Week 26	148 to 270	182
	6	Month 12	271 to 450	360
	7	Month 18	451 to 630	540
	8	Month 24	631 to 810	720
	9	Month 30	811 to 990	900
	10	Month 36	991 to 1170	1080
	11	Month 42	1171 to 1350	1260
	12	Month 48	1351 to 1530	1440
	13	Month 54	1531 to 1710	1620
	14	Month 60	1711 to 1890	1800
	x	Month n	n×30-89 to n×30+90	n×30

*Relative to Study Day 1 (Section 5.1.3).
**Visit x corresponds to an interval of every 6 months.

For safety analysis, only assessments measured during the treatment period (i.e., from study intervention start up to 3 days after study intervention discontinuation, limits included) are considered in the time interval of Month n (i.e., an interval of every 6 months).

5.1.2. Study Day and Relative Day

Study day or relative day for a visit is defined as:

- Visit date - date of Study Day 1 + 1, if visit date ≥ date of Study Day 1
- Visit date - date of Study Day 1, if visit date < date of Study Day 1

There is no 'Day 0'.

The Study Day 1 for OLS and STS periods is defined in Sections 5.1.3.1and 5.1.3.2.

5.1.3. Study Day 1 and End of Treatment

5.1.3.1. For Treated Set - OL

Study Day 1 (or Day 1) refers to the start date of the first study intervention administration in A303, as defined in Section 4. If the start date is missing, the date of Visit 1 in CRF will be used.

End of treatment (EOT) refers to the date of the last selexipag administration in A303.

5.1.3.2. For Selexipag treated Set

Study Day 1 (or Day 1) refers to the start date of the first selexipag administration in either A302 or A303 (whichever is earlier), as defined in Section 4. If the start date is missing, the date of Visit 1 of A302 or A303 (whichever is earlier) in CRF will be used.

EOT refers to the date of the last selexipag administration in A302 or A303, whichever is later.

5.1.4. Last Contact Day

5.1.4.1. For A302 Participants not Entered in A303

The last contact date is defined as the latest of the following dates: Adverse Event start date; Hospitalization admission date; Death date; Any event date confirmed by the CEC; Clinical Worsening Event date; Study Intervention start / end dates; Disposition dates (from the CRF pages: "Survival Follow-up at Study Closure", "Post-Treatment Observation Closure Visit"); and any visit-based assessments such as, but not limited to: ECG, laboratory, vital signs, 6MWT or questionnaires (Camphor, WHO FC, Borg Dyspnea score, etc.).

5.1.4.2. For A302 Participants Entered in A303

The last contact date is taken directly from A303 CRF page 'Study completion'. If missing, the last contact date is defined as the latest of the following dates: Adverse Event start date; Death date; Study Intervention start / end dates; Visit dates (from the CRF page "Visit Log"); Disposition dates (from the CRF page "End of Study Visit"); and any visit-based assessments such as, but not limited to laboratory or vital signs.

5.1.5. Baseline definition

5.1.5.1. For Treated Set - OL

Baseline is defined as the last observation prior to or on the respective Study Day 1 (Section 5.1.3.1) of selexipag treatment start in A303.

5.1.5.2. For Selexipag treated set

Baseline is defined as the last observation prior to or on the respective Study Day 1 (Section 5.1.3.2) of selexipag treatment start in A302 or A303.

5.1.6. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates in A302 and A303 will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the AE onset is different from the month/year of the study intervention start
  - The day of study intervention start (A302/A303), if the month/year of the AE onset is the same as month/year of the study intervention start date and month/year of the AE resolution date is different
  - The day of study intervention start or day of AE resolution date, whichever is earliest, if month/year of the AE onset and month/year of the study intervention start date and month/year of the AE resolution date are the same
- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of AE onset, as long as this date is on or after the study intervention start date
  - Month and day of the study intervention start date, if this date is in the same year as the AE onset
  - Last day of the year if the year of the AE onset is prior to the year of the study intervention start date
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

If the AE resolution dates is partial it will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of resolution or the day of the death date, if the death occurred in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the death date, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

The approach described above (the Janssen standard approach) will give reasonable imputed values for partial missing onset dates.

5.2. Participant Dispositions

The following disposition categories (derivable from 'Study Completion' page of CRF) will be summarized (taking the information from the last available A302/A303 study) for both OLS and STS (A302+A303):

- Participants who completed the study (attended EOS visit)
- Participants who terminated study participation prematurely
- Reason for termination of study participation*^
- Participants who completed study intervention

- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention*^

NOTE: *The A302 protocol has “end of study” (EOS) visit before the “end of treatment in TEP (Treatment Extension Period)” visit. The reason(s) for discontinuation of study intervention / termination of study will be taken from the last available information (at EOS or end of TEP visit) in A302.

^Unknown reason for discontinuation will be summarized by “Chinese participants” and “Other participants”.

A listing of participants who terminated study participation prematurely will be generated, separately, for OLS and STS (A302+A303) .

A listing of participants who discontinued study treatment prematurely will be generated, separately, for OLS and STS (A302+A303).

5.3. Primary Endpoint(s) Analysis

No primary efficacy endpoint.

5.4. Secondary Endpoint(s) Analysis

No secondary efficacy endpoints.

5.5. Safety Analyses

All safety analyses will be summarized using OLS and STS (A302+A303) based on actual treatment received, unless otherwise specified. All results of OLS and STS (A302+A303) will be summarized in the same tables as displayed in Section 4, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Additional analyses are specified in Section 5.5.3.

5.5.1. Extent of Exposure

Study intervention duration in days is defined as [End date of study intervention] – [Start date of study intervention] +1 (Section 5.1.3), and in months as (duration in days / 30.4). Subject-years of treatment are calculated as (duration in days/ 365.25). The total subject-years of a treatment group is the sum over individual participants of that treatment group.

The number and percentage of participants who receive the study intervention will be summarized. Study intervention duration and subject-years of treatment will be summarized with N, mean, SD, median, and range (minimum, maximum).

In addition, frequency for participants with cumulative study intervention duration ≥1 month, ≥3 months, ≥6 months, ≥12 months (every 12 months after this) will also be summarized.

Descriptive statistics of study intervention duration will be presented overall as well as by categories of Individual Maximum Tolerated Dose (IMTD), as defined in Section 5.5.1.1. In addition, descriptive statistics for IMTD will be presented, overall and by categories of IMTD (Section 5.5.1.1).

5.5.1.1. Definition of IMTD

The IMTD (mcg b.i.d.) is defined by the following rules regardless of length of the titration period:

- Participants who entered the study defined maintenance period (=who completed the study titration period, Section 6.10):
  - IMTD is defined as the last b.i.d. dose at the end of titration period
- Participants who did not enter the study defined maintenance period (=who withdrew from the study during the study titration period, Section 6.10):
  - IMTD is defined as the highest b.i.d. dose without dose reduction afterward.
  - If no up-titration attempted, IMTD is defined as zero.

The IMTD (mcg b.i.d.) categories are defined for both STS (A302+A303) and OLS as

- 0
- 200-400
- 600-1000
- 1200-1600

5.5.1.2. Treatment-emergent Exposure Durations

For estimating the average annualized event rates of treatment-emergent adverse events of special interest (Section 5.5.2.2 and 5.5.2.3), the treatment-emergent (TE) exposure durations (in days) of individual participants are required and calculated as [EOT+ 3 days] – Day 1 + 1 day. The TE exposure duration in months is calculated as (duration in days / 30.4) and in years (also called TE subject-years) as (duration in days / 365.25). The total TE exposure duration of a treatment group is the sum over individual participants of that treatment group, and the average TE exposure duration is the total duration divided by the number of participants of that treatment group.

For prostacyclin associated reactions (Section 5.5.2.3), additional TE exposure durations of individual participants are defined for the titration and maintenance periods.

- The TE exposure duration of the titration period will be calculated as:
  - If the participant did NOT prematurely stop the study intervention before Day 86: TE exposure duration (days) = 86.
  - If the participant prematurely stopped the study intervention before Day 86: TE exposure duration (days) = [EOT+ 3 days] – [Day 1] + 1 (Section 5.1.3).
- The TE exposure duration of the maintenance period will be calculated as:

- If the participant did NOT prematurely stop the study intervention before Day 86: TE exposure duration (days) = {[EOT +3 days] – [Day 1] + 1} – 86 (Section 5.1.3).

- If the participant prematurely stopped the study intervention before Day 86: TE exposure duration will not be calculated, and the participant will be excluded from the denominator.

For a period (titration or maintenance) the TE subject-years of individual participants are calculated as (period-specific duration in days / 365.25). The total TE subject-years for a period of a treatment group is the sum over individual participants included in the respective period of that treatment group.

5.5.2. Adverse Events

Any events recorded on the AE pages of the A303 CRF or A302 CRF.

5.5.2.1. Treatment-Emergent Adverse Events

Definition: The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the MedDRA, version 22.0. Any AE occurring at or after the initial administration of study intervention (on Day 1 in STS [A302+A303] or OLS – see Section 5.1.2) through EOT plus 3 days is considered as treatment emergent (TE). If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events (TE-AEs) will be included in the analysis.

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Binary variables, occurrence for each of the following categories of TE-AEs, TE-SAEs and SAEs (Yes/No):

- All TE-AEs
- TE-Serious AEs (TE-SAEs), including fatal (by the tick box 'Yes' for 'Serious' in CRF)
- All SAEs occurring at or after the initial administration of study intervention through EOT plus 30 days (instead of plus 3 days as for TE-SAEs)
- TE-AEs leading to discontinuation of study intervention (by the tick box 'Permanently discontinued' for 'Action taken with study drug' in CRF)
- TE-AEs by severity (by ‘Maximum intensity’ in CRF)
- TE-AEs by relationship to study intervention (defined as ‘Related’ or ‘Unrelated’ in CRF)
- TE-AEs leading to fatal outcome (by the tick box 'Death' for 'Outcome' in CRF)
- TE-AEs and TE-Serious AEs associated with COVID-19 infection.

- TE-AEs associated with COVID-19 infection leading to fatal outcome.

Summary method(s) for outcome measure:

- The (crude) incidence proportion defined as the percentage of participants who experienced at least 1 occurrence of a specific AE divided by the total number of participants.
- All categories of TE-AEs will be summarized by SOC and PT, whereby the PT "Disease Progression" is only reported, if it is the only PT that the respective AE is coded to. The categories of All TE-AEs, TE-SAEs and SAEs will also be summarized by PT. An overall summary of all TE-AE categories will be provided. This will include the TE-AEs associated with COVID-19 infection. TE-AEs associated with COVID-19 infection will be reported for OLS only.
- The exposure-adjusted incidence rate (EAIR) will be summarized by SOC and PT. TE-EAIR is defined as the number of participants exposed to the intervention and experiencing a certain event divided by the total exposure duration of all participants who are at risk for the event. Specifically, for participants with no such event, the at-risk exposure duration is calculated from the Day 1 to EOT + 3 days; for participants with at least one event of a certain SOC or PT, the at-risk exposure duration is calculated from Day 1 to the first onset of such event.
- The TE-AE summaries above will also be reported for subgroups by PAH medication at baseline - Group 1 (defined in Section 5.6.8).
- TE-Serious AEs will also be summarized, by SOC and PT. In addition, serious TE-AEs will be summarized for subgroups by PAH medication at baseline - Group 1 (defined in Section 5.6.8).
- TE- AEs leading to discontinuation of study intervention will also be summarized, by SOC and PT. In addition, they will be summarized for subgroups by PAH medication at baseline - Group 1 (defined in Section 5.6.8).
- Severe TE-AE will also be summarized, by SOC and PT. In addition, severe TE-AEs will be summarized for subgroups by PAH medication at baseline - Group 1 (defined in Section 5.6.8).
- Related TE-AE will also be summarized, by SOC and PT. In addition, related TE-AEs will be summarized for subgroups by PAH medication at baseline - Group 1 (defined in Section 5.6.8).
- TE- AEs leading to fatal outcome will also be summarized, by SOC and PT. In addition, they will be summarized for subgroups by PAH medication at baseline - Group 1 (defined in Section 5.6.8).
- TE-Serious AEs associated with COVID-19 infection will also be summarized, by PT. The summary will report data from OLS only.
- TE-AEs associated with COVID-19 infection leading to death will be summarized too, by PT and for OLS only.

Listings of all AEs, SAEs and AEs with fatal outcome will be generated, separately, for STS (A302+A303) and OLS.

5.5.2.2. Adverse Events of Special Interest

Definition: See Section 6.8 for the list of adverse events in each adverse events of special interest (AESI) category. Any AESI occurring at or after the initial administration of study intervention (in STS or OLS – see Section 5.1.3) through EOT plus 3 days is considered as treatment emergent.

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Binary variables, occurrence of each category (Section 6.8) of treatment-emergent adverse events of special interest (TE-AESI), (Yes/No):

Summary method(s) for outcome measure:

- Number and percentage of participants with at least one TE-AESI.
- Number and percentage of participants with at least one TE-AESI leading to discontinuation of study intervention.
- Number and percentage of participants with at least one serious TE-AESI.
- Number and percentage of participants with at least one TE-AESI with a fatal outcome.
- Number of recurrent TE-AESIs (Participants may have multiple preferred terms [PTs] under a TE-AESI or/and multiple occurrences of a PT. The total number of occurrences of any PT in each TE-AESI category will be used).
- Total TE subject-years of treatment (Section 5.5.1)
- Average annualized event rate is calculated as the sum of numbers of recurrent TE-AESIs of individual participants in a treatment group/total TE subject-years of treatment
- Observed PTs (if a participant had multiple occurrences of a PT, this participant is counted only once)
- Severity (if a participant had multiple occurrences of a PT with different severity levels, this participant is counted only once in the worst severity level)

Separate listings of TE-AESIs will be generated for STS (A302+A303) and OLS.

5.5.2.3. Treatment-Emergent prostacyclin associated reactions

Definition: The detailed definition of TE prostacyclin associated reactions (i.e., selected TE-AEs) is given as one of the AESI categories in Section 6.8. In addition, TE-AEs during each period are defined as:

- TE-AEs in the titration period (Section 6.10): Any prostacyclin associated reaction that occurred at or after the initial administration of study intervention through Day 86, or EOT plus 3 days for participants who discontinued study intervention in the titration period.

- TE-AEs in the maintenance period (Section 6.10): Any prostacyclin associated reaction that occurred at or after Day 87 through EOT plus 3 days. Participants who discontinued during the titration period are excluded from the denominator.

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Binary variables, occurrence of TE-prostacyclin associated reactions (Yes/No)

Summary method(s) for outcome measure:

- The same analysis applied for TE-AESI in "Summary method(s) for outcome measure" paragraph (Section 5.5.2.2).
- All TE-prostacyclin associated reactions will also be reported for subgroups by PAH medication at baseline - group 1 (defined in Section 5.6.8)
- All TE-prostacyclin associated reactions will also be reported separately for the titration period and the maintenance period. Participants who entered A303 might have experienced a titration period in A302 and another titration period in A303; in this case the rule in Section 6.10 is followed.
- Total TE subject-years will also reported separately for the titration period and the maintenance period (Section 5.5.1.2).

5.5.2.4. Death

Definition: Any death recorded on the Study completion page of the A302 or A303 CRF.

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Binary variables, occurrence of death (Yes/No):

- Treatment emergent death (until EOT plus 3 days)
- Death up to safety follow-up (until EOT plus 30 days)
- All death (regardless of the time frame)

Summary method(s) for outcome measure:

- Number and percentage of participants who died
- Cause of death (for deaths due to multiple causes, their frequencies will be included in each relevant cause)

The summary of deaths (i.e., until EOT plus 30 days) will also be reported for subgroups by PAH medication at baseline - group 1 (defined in Section 5.6.8). Separate listings of all deaths will be generated for STS (A302+A303) and OLS.

5.5.2.4.1. Survival Analysis

Definition: Time to death is calculated from the initiation of selexipag in A302 to death. Participants who died after initiation of selexipag are considered having an event. For the remaining participants their times to death are censored, with the censoring date defined as the latest date between date of completion/discontinuation/lost to follow-up and the last contact date (see Section 5.1.4 for definition).

The median follow-up time will be estimated using the reverse Kaplan-Meier (KM) estimate of survival data, i.e., reversing censoring indicator for the KM estimate, with CENS = 0 for death and CENS = 1 for being alive.

Population: Subset of participants who received selexipag in A302 in the STS (A302+A303).

Study Intervention: Selexipag

Outcome measures: Time to death (regardless of the time frame) from start of first selexipag dose to A303 Study Closure

Summary method(s) for outcome measure:

- Descriptive summary (i.e., number of participants at risk, number of participants censored, number of deaths)
- KM estimates with point estimate (%) and 95% confidence limits (CLs). It will be provided at every three months in the 1st year, and every year thereafter. The CLs are constructed using Greenwood's formula (Collett 2014) for the standard error.
- KM estimates will also be displayed graphically. The KM curve will be truncated when less than 10% of the initial participants remain at risk (Pocock 2002).
- Additional subgroup analyses by baseline WHO FC (group 2):
    - Descriptive summary and KM estimates with 95% CLs for each WHO FC (I/II/III/IV).
    - Separate KM curves for WHO FC II and III

A sensitivity analysis for deaths up to EOT + 30 days will be performed as defined in Table 5 below.

Table 5: Sensitivity Analysis

- **Population:** For participants who died or were known alive after EOT + 30 days, the time to death will be censored at the earliest date between EOT + 30 days and the last contact date (see Section 5.1.3.1 for definition). - **Outcome measures:** Time to death from start of first selexipag dose to EOT + 30 days. - **Summary method(s) for outcome measure:** Same as survival analysis described above.

5.5.3. Additional Safety Assessments

5.5.3.1. Clinical Laboratory Tests

Definition: A post-baseline abnormality (based on criteria defined in Table 6) will be considered treatment emergent if it is worse than the baseline abnormality and assessed after the initial administration of study intervention (on Day 1) and no later than EOT plus 3 days. If the baseline abnormality information is missing, the abnormality is always considered treatment emergent. If the post-baseline value is above the upper limit and the baseline value is below the upper limit, then the post-baseline abnormality will be considered treatment emergent. The same applies to the post-baseline value being below the lower limit and the baseline value being above the lower limit. However, a post-baseline abnormality that is in the same category of abnormality already existing at baseline will not be counted as treatment emergent. For example, if a participant already has "marked abnormality" in hemoglobin at the (re-)baseline, (s)he will have TE "alert abnormality" when at least one of the post-baseline values meets the hemoglobin alert criteria. But (s)he will not have TE "marked abnormality" regardless of the post-baseline values, and this participant will be excluded from the denominator of TE marked abnormality in hemoglobin.

For each analysis set, the worst post-baseline abnormal (for both above or below the normal range) result of a parameter is considered. Unscheduled visit results are also included.

Table 6: Definition of Abnormalities for Hematology and Chemistry Test

Parameter (SI unit)	LL Marked	LLL Alert	HH Marked	HHH Alert
Hemoglobin (g/L) baseline within ULN baseline above ULN	 < 100 < 100	 < 80 < 80	 > 20 above ULN > 20 above baseline	 > 40 above ULN > 40 above baseline
Hematocrit (L/L) males females	 < 0.32 < 0.28	 < 0.20 < 0.20	 > 0.60 > 0.55	 > 0.65 > 0.65
Platelets (10^9/L)	< 75	< 50	> 600	> 999
Leucocytes (10^9/L)	< 3	< 2	> 20	> 100
Neutrophils (10^9/L)	< 1.5	< 1.0	-	-
Eosinophils (10^9/L)	-	-	> 5	-
Lymphocytes (10^9/L)	< 0.8	< 0.5	> 4	> 20
ALT	-	-	> 3 ULN	> 5 ULN
AST	-	-	> 3 ULN	> 5 ULN
Alkaline Phosphatase	-	-	> 2.5 ULN	> 5 ULN
Direct Bilirubin	-	-	> 2 ULN	> 5 ULN
Total Bilirubin	-	-	> 2 ULN	> 5 ULN
Creatinine baseline within ULN baseline above ULN	 - -	 - -	 > 1.5 ULN > 1.5 baseline	 > 3 ULN > 3 baseline
Glucose (mmol/L)	< 3	< 2.2	> 8.9	> 13.9
Sodium (mmol/L)	-	< 130	> 150	> 155
Potassium (mmol/L)	< 3.2	< 3	> 5.5	> 6
Urea (mmol/L)	-	-	> 2.5 ULN	> 5 ULN
Albumin	< 30	< 20	-	-
Creatinine Clearance/eGFR (mL/min)	< 60	< 30	-	-
BUN	-	-	> 2.5 ULN	> 5 ULN

ULN = upper limit of the laboratory normal range. This table is based on Actelion OTH-000005 version 09.
Laboratory parameters collected in a study level are not always the same across studies. Some of the parameters listed above might not be applicable in certain studies.

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Treatment emergent markedly abnormal laboratory values.

Summary method(s) for outcome measure:

- Number and percentage of participants with treatment-emergent markedly abnormal laboratory values will be presented by treatment group over time.
- The treatment-emergent laboratory abnormalities will also be reported for subgroups by PAH medication at baseline - group 1 (defined in Section 5.6.8).
- Descriptive summary statistics by visit are displayed for observed values and absolute changes from baseline to each visit for hematology and blood chemistry laboratory tests from the central laboratory. Separate tables for STS and OLS will be produced.

- The descriptive summaries and changes from baseline as specified above will also be reported for subgroups by PAH medication at baseline - group 1 (defined in Section 5.6.8). Separate tables for STS and OLS will be produced.

If a parameter is not analyzed in A302 or A303, it will be reported only in the study that is applicable, e.g., lymphocytes is collected in A302 only, it will be summarized/listed under STS (all from A302) and empty in OLS.

Separate listings of markedly abnormal laboratory values (by group of parameters) will be provided for STS (A302+A303) and OLS.

Additionally, listings of all available laboratory values (by group of parameters) will be provided for STS (A302 + A303) and OLS, separately. The available laboratory parameters are shown in Table 7 below.

Table 7: Laboratory parameters

Parameter (SI unit)	
1. ALT (IU/L)	15. Glucose (mmol/L)
2. Albumin (g/L)	16. Hematocrit (L/L)
3. Alkaline Phosphatase (IU/L)	17. Hemoglobin (g/L)
4. AST (IU/L)	18. Leucocytes (10^9/L)
5. Basophils (10^9/L)	19. Lymphocytes (10^9/L)
6. Basophils/Leukocytes (%)	20. Lymphocytes/Leucocytes (%)
7. Total Bilirubin (µmol/L)	21. Monocytes (10^9/L)
8. Direct Bilirubin (µmol/L)	22. Monocytes/Leucocytes (%)
9. Blood Urea Nitrogen (mmol/L)	23. N-Terminal ProB-type Natriuretic Peptide (ng/L)
10. Creatinine (µmol/L)	24. Neutrophils (10^9/L)
11. Creatinine Clearance (mL/min)	25. Neutrophils/Leucocytes (%)
12. Eosinophils (10^9/L)	26. Platelets (10^9/L)
13. Eosinophils/ Leucocytes (%)	27. Potassium (mmol/L)
14. Erythrocytes (10^{12}/L)	28. Sodium (mmol/L)

5.5.3.1.1. Abnormalities in liver function test results

Additional analyses for TE abnormalities in liver function tests will be performed.

Definition: Additional abnormalities in liver function tests are defined as follows (the "and" conditions do not require concomitant values):

1. AST > 3 × ULN or ALT > 3 × ULN
2. AST > 5 × ULN or ALT > 5 × ULN
3. AST > 8 × ULN or ALT > 8 × ULN
4. ALT > 3 × ULN and total bilirubin > 2 × ULN
5. (AST > 3 × ULN or ALT > 3 × ULN) and total bilirubin > 2 × ULN.

Abnormality criteria will be applied to baseline and post-baseline values.

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Abnormalities in liver function tests.

Summary method(s) for outcome measure:

- Number and percentage of participants with TE abnormalities
- Abnormalities in liver function tests will also be reported for subgroups by PAH medication at baseline - group 1 (defined in Section 5.6.8).
- A listing and an eDISH plot will be produced to show possible cases as specified in the 4th and 5th abnormalities numbered items. Separate listings and eDISH plots will be produced for STS and OLS.

Separate listings of markedly abnormal values of ALT and AST will be provided for STS (A302+A303) and OLS.

5.5.3.2. Vital Signs

Definition: Vital signs, including blood pressure (systolic and diastolic) and heart rate, is recorded on the Vital Signs page of the A302/A303 CRF. Treatment-emergent vital signs abnormalities are defined as any new vital signs abnormalities reported after baseline (Section 5.1.5) in A302/ A303 and up to EOT plus 3 days. Markedly abnormal vital signs during intervention are defined in Table 8.

Table 8: Markedly Abnormal Vital Signs

Vital Sign	Criteria	
Systolic blood pressure	SBP < 90 mmHg	Or all four notable criteria fulfilled
	Decrease of > 40 mmHg in SBP from baseline	
Diastolic blood pressure	DBP < 50mmHg	
	Decrease of > 20 mmHg in DBP from baseline	

Population: All participants included in the STS (A302+A303) and OLS

Study Intervention: Selexipag

Outcome measures: Continuous vital sign parameters.

Summary method(s) for outcome measure:

- Continuous vital sign parameters will be summarized at each visit with descriptive statistics.
- Change from baseline to each visit will be summarized with descriptive statistics.
- Incidence of treatment-emergent markedly abnormal vital signs during study intervention for participants who had a baseline assessment and at least 1 post baseline assessment for that vital sign, at each visit and overall at any time.

A listing of participants with treatment-emergent markedly abnormal vital signs will be presented, along with a listing of all vital sign measurements. The listings will be presented separately for STS and OLS.

5.5.3.3. Electrocardiogram

Not applicable.

5.5.3.4. Other Safety Parameters

Not applicable.

5.6. Other Analyses

5.6.1. Pharmacokinetics

Not applicable.

5.6.2. Immunogenicity

Not applicable.

5.6.3. Pharmacodynamics

Not applicable.

5.6.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

5.6.5. Biomarkers

Not applicable.

5.6.6. Health Economics

Not applicable.

5.6.7. Other Variables and/or Parameters

Not applicable.

5.6.8. Definition of Subgroups

The following subgroup will be used for some of the safety endpoints, i.e., TE-AE, TE-SAE, severe TE-AEs, related TE-AEs, TE-AESIs, Death and TE- marked laboratory abnormalities.

Subgroup	Definition
*Concomitant PAH-specific medication (group 1), Section 6.5	• No PAH-specific medication (ERA or PDE5-I) • Endothelin receptor antagonist (ERA) alone • Phosphodiesterase 5 inhibitor (PDE5-I) alone • Combination of both ERA and PDE5-I

*For both STS (A302+A303) and OLS, this variable should be re-baselined according to Sections 6.3 and 5.1.5

In addition to the subgroups defined above, the following "potential" subgroups defined by selected baseline characteristics will be set up in the ADaM dataset.

(Potential) Subgroup	**Definition**
Gender	• Male • Female
*Age Group at baseline (years)	• [<18] • [18-64] • [65-74] • [75-84] • [≥85]
*WHO Functional Class at baseline (group 1)	• I/II • III/IV
*WHO Functional Class at baseline (group 2)	• I • II • III • IV
*Concomitant PAH-specific medication (group 2)	• No PAH-specific medication • 1 PAH-specific medication • ≥ 2 PAH-specific medications The number of PAH specific medications (type) is based on following 4 types. - ERA - PDE5-I - sGC stimulator - Prostacyclin
Etiology	• Idiopathic, heritable, drug or toxin induced, associated with HIV infection • Associated with connective tissue disease • Associated with congenital heart disease with corrected systemic-to-pulmonary shunts
*Antithrombotic medication at baseline	• No antithrombotic medication • Presence of antithrombotic medication

*For both STS (A302+A303) and OLS, these variables should be re-baselined according to Sections 6.3 and 5.1.5

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
BL	baseline
BMI	body mass index
BUN	Blood Urea Nitrogen
CDDM	Clinical Development Data Management
CEC	Critical Event Committee
CLs	confidence limits
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSR	Clinical Study Report
DPS	Data Presentation Specifications
DSUR	Development Safety Update Report
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
ERA	endothelin-receptor antagonist
FDA	Food and Drug Administration
HGR/HGRAO	Human Genetic Resources/ Human Genetic Resources Administration Office
HPAH	Heritable Pulmonary Arterial Hypertension
IB	Investigator Brochure
ICE	Integrated Computer Environment
IMTD	Individual Maximum Tolerated Dose
INR	International Normalized Ratio
IPAH	Idiopathic Pulmonary Arterial Hypertension
IQ	interquartile
KM	Kaplan Meier
MAA	Marketing Authorization Application
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	AC-065A303/GRIPHON OL
OLS	Treated Set – OL
OSB	Ophthalmology safety board
PAH	Pulmonary Arterial Hypertension
PBRER	Periodic Benefit-Risk Evaluation Report
PDs	Protocol Deviation
PDE5-I	phosphodiesterase type 5 inhibitor
PT	Preferred term
RDB	AC065A302/GRIPHON - Randomized Double Blind
RMP	risk management plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCS	Summary of Clinical Safety
SD	standard deviation
SDG	Standard Definition Group
sGC	Soluble guanylate cyclase

SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
STS	Selexipag Treated Set
TE-AEs	treatment-emergent adverse event
TE-SAEs	treatment-emergent serious adverse event
ULN	upper limit normal
WHO FC	World Health Organization Functional Class
WHO-DD	World Health Organization Drug Dictionary
6MWD	Six Minute Walk Distance

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Analysis of Exposure (Sections 5.5.1 and 5.5.1.1) by IMTD is included. Reason: The definition and analysis are in line with the original NDA/MAA submission in 2014 as well as supplemental NDA/MAA submission for long-term safety and survival in 2020, and the RMP version 8.1 support to 5-year MAA renewal. In both submission dossiers, the A303 data were already pooled with A302.

To prevent a violation of China's Human Genetic Resources (HGR) regulation, data participants in China for A303 that were due beyond 20 December 2019 are either not collected in clinical database or will be excluded from SDTM.

Protocol deviations (PDs) (Section 6.4) include also COVID-19 and HGRAO (Chinese HA) related PDs.

6.3. Appendix 3 Demographics and Baseline Characteristics

Table 9 lists the demographic variables that will be summarized.

Table 9: Demographic Variables

Continuous Variables	**Summary Type**
^Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
^Weight (kg)	
Height (cm)	
^Body Mass Index (BMI) (kg/m^2)	
^6MWD (m)	
^NT-proBNP (ng/L)	
^Time since diagnosis (years)	
Categorical Variables	
^Age (<18 years, 18-64 years, 65-74 years, 75-84 years, and ≥85 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Race/ethnicity (Caucasian /Hispanic, Asian, Black, Other)	
Geographical regions (Asia, Eastern Europe, Western Europe + Australia, North America, Latin America)	
^BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2)	
Etiology (Idiopathic (IPAH), Heritable (HPAH), Drug or Toxin Induced, Assoc. with Connective Tissue Disease, Assoc. with Congenital Heart Disease, Associated with HIV Infection)	
^WHO-FC (I, II, III, and IV)	
^Concomitant PAH medication at BL (None, ERA alone, PDE5i alone, ERA+ PDE5i)*	
^NT-proBNP (low <300 ng/L, medium 300 =< - =< 1400 ng/L, high > 1400ng/L)	
^Number of low-risk criteria met at baseline (0, 1, 2, 3)**	
^Antithrombotic medication at baseline	

[a] If multiple race categories are indicated, the Race is recorded as 'Other'.
*Details of PAH medication at baseline are presented in Section 6.5.

**Low risk criteria met at baseline are: NT-proBNP < 300 ng/L, WHO functional class equal to I/II, 6MWD > 440m.

^For both STS (A302+A303) and OLS, these variables should be re-baselined according to Section 5.1.5.

Some baseline characteristics (specified with symbol ^ in Table 9 above) should be re-baselined according to the analysis set used: for STS (A302+A303), baseline covariates were assessed prior to the start of selexipag; for OLS they were assessed prior to the start of selexipag in A303 (Section 5.1.5). Especially for age, the following formula will be used: age in years at A302 screening date – year of A302 screening date + year of A303 start of intervention.

Demographic variables will be summarized separately for STS and OLS. For OLS, they will be summarized showing all treatment sequences:

	Treated Set - OL (A303) ^					
	Ex-Selexipag 330		Ex-placebo 379		Total A303 709	
	BL at A302	BL at A303	BL at A302	BL at A303	BL at A302	BL at A303

^Participants treated in A303.

Separate listings of demographic variables for STS and OLS will also be produced.

6.4. Appendix 4 Protocol Deviations

PDs are defined in the following document: TV-eFRM-06818.

PDs s are listed and summarized displaying counts and percentages of participants with at least one PD. A similar table is presented for major PDs. Only data of OLS (A303) will be summarized.

The PDs in the summary tables will be sorted by overall frequency, in descending order; if a tie occurs, the tied characteristics will be sorted alphabetically.

All reported PDs will be described in a participant's listing. Major PDs will be flagged accordingly.

Protocol deviations related to COVID-19 will be summarized for all such PDs and for major such PDs on OLS and also be presented in a listing.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). These medications are recorded on the 'Previous/Concomitant Medication' pages of the A302 and A303 CRF. Prior medications are defined as any therapy used before the day of the first dose of study intervention. Concomitant medications at baseline are defined as any therapy started on the same day as the first dose of study intervention, or before and continued after the first dose of study intervention. Concomitant medications started during intervention are defined as any therapy started after the day of the first dose of study intervention (excluding medication started after the end of study intervention). Handling missing data is defined in Section 6.5.1.

For A302 general prior medications and concomitant medications were already reported in the A302 CSR. General concomitant medications in A303 are not of interest and will not be summarized. Only listings of all concomitant medications at baseline or started during study intervention will be generated separately for OLSs and STS (A302+A303).

Concomitant PAH-specific medications will be summarized by ingredient name and PAH-specific medication group name (Table 10) using grouping 1 and 2 as defined in Section 5.6.8. For each of the following 2 types of concomitant PAH-specific medications, summary of OLS and STS (A302+A303) will be presented in the same table according to Section 4.

- Concomitant PAH-specific medications at baseline, i.e., any therapy used on the same day as the first dose of study intervention and might continue after the first dose of study intervention). For the STS (A302+A303), baseline refers to the first dose of selexipag either in A302 (participants who received selexipag in A302) or in A303 (participants who received placebo in A302).
- Concomitant PAH-specific medications started during study intervention.

Listings of PAH specific concomitant medications at baseline or started during study intervention will be generated separately for OLS and STS (A302+A303).

Additionally, the following will be summarized separately for OLS and STS (A302 + A303):

- Number of participants who added a post-baseline new class of PAH-specific medication. A post-baseline new class of PAH-specific medication is defined as any new class of PAH therapy (i.e., ERA/PDE5-i/sCG stimulator/Prostacyclin and analogs only; ERA+PDE5-i; ERA+sCG stimulator; ERA+Prostacyclin and analogs, PDE5-i+sCG stimulator, sCG stimulator+Prostacyclin and analogs, etc.) started after baseline (see Section 5.1.5 for the definition of baseline for STS and OLS).
- Duration of exposure in years (i.e., sum of total exposure duration and mean) before, after and without adding a post-baseline new class of PAH-specific medication.
- Duration of exposure before and after adding a new class of PAH therapy will be given for participants who added at least 1 post-baseline new class of PAH therapy. Exposure duration before adding a new class of PAH therapy will be computed as (start of new class of PAH therapy - start of treatment) / 365.25; Exposure duration after adding a new class of PAH

therapy will be derived as (end of treatment - start of new class of PAH therapy+1) / 365.25. Duration of exposure without addition of a new class of PAH therapy will be given for the number of participants with (or without) concomitant PAH therapy at baseline minus the number of participants who added at least 1 post-baseline new class of PAH therapy, and will be computed as (end of treatment - start of treatment+1) / 365.25.

Table 10: PAH Specific Therapies

Group name for the Analysis outputs	Category	Subcategory	Generic names
ERA	Antihypertensives for pulmonary arterial hypertension	ERA	ambrisentan, bosentan, sitaxentan, macitentan
PDE5-i		PDE-5 Inhibitor	sildenafil, tadalafil, vardenafil, udenafil
sCG stimulator		sGC stimulator	riociguat
Prostacyclin/prostacyclin agonists	Prostanoids		epoprostenol, treprostinil, iloprost, beraprost
Categories are identified by searching the coded WHODRUG preferred terms for occurrence of any of the ingredient names. E.g., 'Sildenafil' and 'Sildenafil Citrate' will both be assigned to sildenafil and thus both considered as PDE-5 inhibitors.			

6.5.1. Imputation Rules for Missing Start/End Date of Concomitant Medication

Incomplete and missing start dates of medication in A302/A303 will be imputed as follows:

- If the end date of the medication is not before the start of study intervention and if the study intervention start falls in the range of possible dates, the start date of the medication is imputed with the study intervention start date. In all the other cases, the start date of the medication is imputed with the lower limit.
- If the start date of the medication is missing, the medication is considered to have started before start of study intervention.

Incomplete and missing end dates of medication in A302/A303 will be imputed as follows:

- If the end date is incomplete, the upper limit is used.
- If the end date is missing: no imputation, the medication is considered ONGOING.

6.6. Appendix 6 Medical History

Not applicable.

6.7. Appendix 7 Intervention Compliance

Not applicable.

6.8. Appendix 8 Adverse Events of Special Interest

The following adverse events of special interest will be used for selexipag. These are based on the important identified and potential risks in the latest Risk Management Plan and on-going discussion with Pharmacovigilance Risk Assessment Committee.

AE Special Interest Category
Anaemia
Bleeding events
Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
Hyperthyroidism
Hypotension
Light-dependent non-melanoma skin malignancies
Major adverse cardiovascular events (MACE)
Medication errors
Ophthalmological effects associated to retinal vascular system
Pregnancy
Pulmonary venoocclusive disease associated with pulmonary oedema
Renal function impairment / acute renal failure
Prostacyclin associated reactions*

*Prostacyclin associated reactions will be summarized separately from other AESIs

Adverse events of special interest are defined in the aesi220.xlsx file available in SPACE.

6.9. Appendix 9 Medications of Special Interest

Anticoagulants and antithrombotic are selected based on the ATC code available in the Standard Definition Group (SDG) Excel file available in SPACE (SDG_B3C3_March1_2020_126.xlsx). The SDG file contains all possible antithrombotic medications in line with the WHO drug dictionary version (March 2020) used in A302 and A303. It will be used to identify the anti-thrombotic medications given during these studies.

6.10. Appendix 10 Titration and maintenance periods

In the A302 CSR SAP, titration and maintenance periods are defined as follows:

- The study intervention Titration Period starts at date of first intake of study intervention and ends at Day 86 (or earlier, if selexipag is discontinued before). Study Day 86 has been chosen according to the study protocol-specified maximum duration of the Titration Period including a 3 days tolerance.
- The study intervention Maintenance Period starts at Day 87 and ends at the date of last intake of study intervention.

Note: The definition of titration/maintenance period in the A303 protocol is not clear, in fact in Section 3.10.2.10 it seems that Week 16 is included in the titration period. For OLS and STS (A302+A303), titration period should be considered to end at Week 12 as defined in the summary of clinical safety (SCS) of the first NDA/MAA submission in 2014. In the A302 protocol, the first dose was to be given in the afternoon at study day 1 with an exposure duration of 0.5 day. Thus, the duration of titration period, for participants who did not prematurely stop the study intervention during the titration period, was considered as 86.5 days in the SCS for the first NDA/MAA. However, for the onset of adverse events only the date (without time) was collected. In addition, data of study drug log in CRF cannot distinguish whether a patient received afternoon dose only or both morning and afternoon doses. Therefore, the SCS for the sNDA/MAA submission in 2020, RMPs and newly completed selexipag studies were summarized without using such half-day convention and the titration period ended at day 86.

Participants who entered A303 might have experienced a titration period in A302 and another titration period in A303. For STS (A302+A303), only the first titration period with Selexipag is taken, i.e., for participants who received Selexipag already in A302, the titration period in A302 is taken; for participants who received Selexipag only in A303, the titration period in A303 is taken.

For OLS, for participants who received Selexipag in A302 and A303, the titration period in A303 is taken; for participants who received Selexipag only in A303, the titration period in A303 is taken. In case a participant received Selexipag in A302 and A303 but without titration in A303, the entire A303 period is considered as maintenance, hence no titration period in OLS.

7. REFERENCES

Collett D. Modelling Survival Data in Medical Research. 3rd ed. New York, NY: Chapman and Hall/CRC; 2014.

Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet. 2002 May 11;359(9318):1686-9.