Janssen Research & Development

Statistical Analysis Plan

A Multicenter, Single-arm, Open-label, Long-term Follow-up Safety Study of Selexipag in Participants who Participated in a Previous Selexipag Study - SOMBRERO

Protocol 67896049PUH3001; Phase 3b

JNJ-67896049 / ACT-293987 (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

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	9 November 2021	Not Applicable	Initial release
2	16 November 2021	Removal of a sentence under 'Frequency of AEs' in Section 5.3.4.	Sentence not applicable
3	27 November 2023	Removal "Selexipag baseline" in Section 5.1.3	After Dry Run the team realized it is not needed

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the methods, conduct and content of statistical analyses of the safety and exploratory endpoints planned for the final Clinical Study Report (CSR).

The following study documents are used for the preparation of the SAP:

- Protocol 67896049PUH3001, Approved version, Amendment 2 Version 3.0, dated 26 October 2021, EDMS-RIM-265923 version 2.0,
- Electronic Case Report Form (eCRF), version 03, dated 27 January 2021,
- Electronic Case Report Form (eCRF) Specifications, version 1.05, dated 05 March 2021.

Source data for the analyses will be provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM).

Analysis Data Model (ADaM) datasets from GRIPHON / GRIPHON OL will be used as additional source data for specific statistical analyses where applicable.

The Data Presentation Specifications (DPS) Part 1 document will be prepared in line with this SAP to provide the list of outputs, layouts and all the programming details necessary to implement the statistical analyses.

The CSR analyses will be performed on the locked database following completion of study by all participants.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the long-term safety of selexipag while providing continued treatment for participants who were previously enrolled in an Actelion-sponsored study with selexipag and who derived benefit from selexipag in indications for which a positive benefit-risk has been established.	• Frequency of AEs • Frequency of AEs leading to premature discontinuation of selexipag • Frequency of serious adverse events (SAEs) • Frequency of deaths • Number of pregnancies with maternal exposure to selexipag These safety endpoints will be assessed continuously from enrollment on Day 1 up to End-of-Study (EOS) visit.
Secondary	
• Not applicable	• Not applicable
Exploratory	
• To capture the long-term dosing pattern of selexipag	• Proportion of participants requiring selexipag dose reduction or increase by reason

1.2. Study Design

This is an open-label, multicenter, long-term, follow-up safety study of selexipag in participants who are currently treated with selexipag at the end of an Actelion-sponsored, interventional study and who benefit from selexipag in indications for which a positive benefit-risk has been established.

The study includes the following consecutive periods:

- **Screening period**: starting with the signature of the informed consent form and ending with the administration of the first dose of the study intervention.
- **Open-label (OL) treatment period**: starting with the administration of the first dose of the study intervention and ending on the day of the last dose of study intervention (EOT). All participants entering the study will continue with the same maintenance dose of selexipag that they were taking during their respective parent study. Participants will present for the EOT visit within 7 days of the last dose of study intervention. For participants rolled over to post-trial access (PTA) or Study NOPRODPAPUH3001 (PLATYPUS), the enrollment must occur on the day of the last visit of SOMBRERO study ie, EOS visit which corresponds to EOT, to avoid selexipag treatment interruption.
- **Post-treatment follow-up period:** starting on the day after the last dose of study intervention and ending 30 days thereafter with the EOS visit. For participants who complete the study treatment and who are eligible for a post-trial access (PTA) program or Study NOPRODPAPUH3001 (PLATYPUS), the post-treatment follow-up period will be waived.

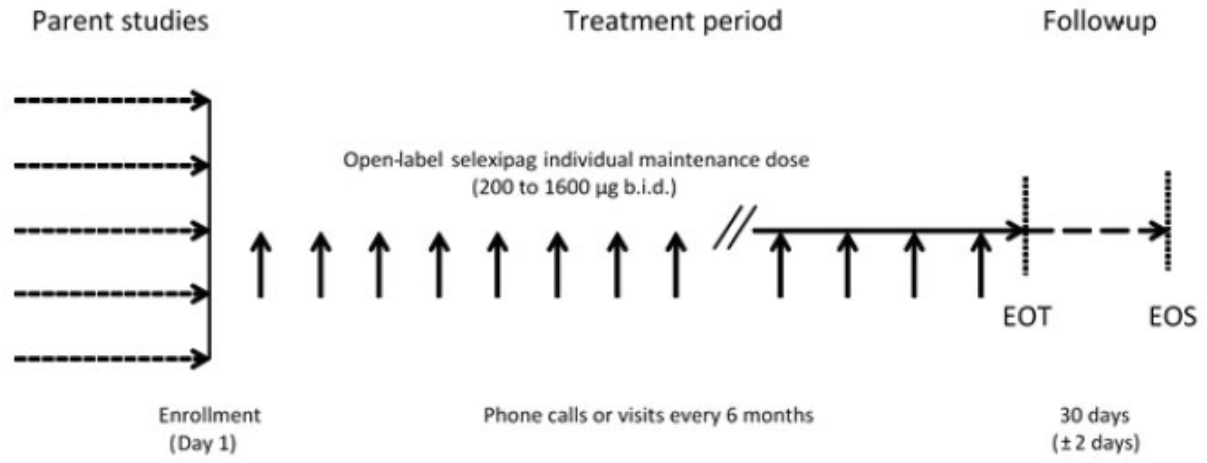
Following enrollment, telephone calls (TCs) or regular visits with the investigator will be scheduled alternatingly every 6 months.

Study intervention re-supply visits will be scheduled every 6 months. For those months when a TC with the investigator is scheduled, the participant may pick up the re-supplies at the study site without meeting with the investigator. The TC will still be required but can be scheduled within the allowed time window.

Participants will present for the EOT visit within 7 days of the last dose of study intervention followed by the EOS visit 30 days after last dose (for participants who complete the study treatment and who are eligible for a post-trial access (PTA) program or Study NOPRODPAPUH3001 (PLATYPUS), the EOS will occur on the same day of EOT).

The overall study design is depicted in Figure 1.

Figure 1 – Schematic Overview of the Study



2. STATISTICAL HYPOTHESES

The objective of the study is to assess the long-term safety of selexipag and no statistical hypothesis will be tested. Only descriptive analyses will be performed and the 95% confidence intervals will be displayed when applicable.

3. SAMPLE SIZE DETERMINATION

Due to the nature and scope of this study, the sample size is not based on statistical considerations. The sample size will be driven by the number of participants still taking selexipag who do not have other options to access selexipag when their respective parent study is completed and who consent to participate in this study. The maximum number of participants currently expected to roll-over from the GRIPHON OL study is approximately 50 participants.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Enrolled	All participants who signed the informed consent form (ICF).
Safety	The safety set includes all enrolled who received at least 1 dose of study intervention in SOMBRERO.

5. STATISTICAL ANALYSES

5.1. General Considerations

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.

The Safety Set will be used for all analyses, if not otherwise specified.

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. Listed below are the analysis visit windows and the target days for each visit. The reference day is Study Day 1 (Section 5.1.2). If a participant has 2 or more actual visits in 1 analysis visit window, the visit closest to the target day will be used as the protocol visit for that analysis 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 an analysis visit window, the later visit is used. If more than one value falls on the same time point (date and time) then the one with the last sequential number in SDTM will be used.

All assignments will be made in chronological order. Once a visit date is assigned to an analysis visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2) are the analysis visit windows and the target days for each visit defined in the protocol. Assessments which fall outside of any planned analysis visit window will not be included in summary tables but will be included into individual participants listings.

Table 2 – Analysis Visit Windows

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Safety and exploratory parameters	1	Baseline	<=1	1
	2	Month 6	2 to 274	183
	3	Month 12	275 to 456	365
	4	Month 18	457 to 638	547
	...			

*Relative to Study Day 1

5.1.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study intervention under this protocol. All safety and exploratory assessments at all visits will be assigned a study day relative to this date.

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

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

There is no 'Day 0'.

5.1.3. Baseline

Baseline of SOMBRERO study is defined as the last value assessed on or before the start date of the study intervention under this protocol. If unscheduled/re-test visits are performed on the day of study intervention start, the available value of the last unscheduled/re-test visit on study intervention start date is considered as baseline.

5.1.4. Signed Informed Consent Date

It is the date of the signed informed consent to this protocol and collected in the "Demographics" eCRF form.

5.1.5. Study Intervention Start Date

Study intervention start date in SOMBRERO is defined as the 'Treatment start date' (the date when the first dose of study intervention in the SOMBRERO study was received) from the first record, in chronological order, recorded in the "Study Drug Administration" eCRF form. If missing, the signed informed consent date will be used.

Selexipag start date is the start date of selexipag from ADaM datasets of GRIPHON (for participants randomized to selexipag in GRIPHON) or GRIPHON OL (for participants randomized to placebo in GRIPHON).

5.1.6. Study Intervention End Date

Also known as the date of study intervention discontinuation, this is the 'Treatment end date' from the last record (defined as the date of the last dose of study intervention intake, i.e. the time of permanent discontinuation of study intervention), in chronological order, recorded in the "Study Drug Administration [Selexipag]" eCRF form where the reason the dose was not administered is ≠ 'TEMPORARILY INTERRUPTED DUE TO AN AE' or 'TEMPORARILY INTERRUPTED NOT DUE TO AN AE'. If the exact date of the last dose is missing, the date of the EOT visit will be used. If the participant is lost to follow-up during treatment, the date of last contact ('Last date known to be alive' from the "Survival Data" eCRF form) will be used.

5.1.7. End of Study

The end of study (EOS) visit is planned at the end of the 30-day post-treatment follow-up. For participants who will complete the study treatment and who will be eligible for a post-trial access (PTA) program or Study NOPRODPAPUH3001 (PLATYPUS), the post-treatment follow-up period will be waived and EOS visit will correspond to EOT in SOMBRERO.

This is the 'Completed date' or 'Discontinued Date' as applicable from the "Trial Disposition (Completion/ Discontinuation)" eCRF form.

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized throughout the study:

- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who terminated study prematurely
- Reasons for termination of study.

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely.

5.3. Primary Safety Endpoints Analyses

The primary objective is to assess the long-term safety of selexipag, hence the primary endpoints are for safety (Section 1.1).

Additional safety analyses for non-primary endpoints are specified in Section 5.5.

5.3.1. Extent of Exposure

The number and percentage of participants who received study intervention will be summarized by dose level at Study Day 1. Additional analyses are specified in the following subsections.

5.3.1.1. Study Intervention Duration

Based on the study intervention start date (Section 5.1.5) and end date (Section 5.1.6), study intervention duration in days for individual participants is defined as:

date of last dose of study intervention – date of first dose of study intervention +1.

The study intervention duration in months is calculated as (days of intervention / 30.4). Participant-years of intervention are calculated as (days of intervention / 365.25).

Descriptive statistics for duration of study intervention will be summarized. Cumulative duration of intervention (≥3 months, ≥6 months, ≥9 months, ≥12 months, then every 12 months where applicable) will be summarized.

5.3.1.2. Treatment-Emergent Exposure Duration

For estimating average annualized event rates of treatment-emergent (TE) adverse events of special interest (AESI, Section 5.3.2.4), the TE exposure durations (in days) for individual participants are required and calculated as

(date of last dose of study intervention + 3) – date of first dose of study intervention +1.

The TE exposure duration in months is calculated as (duration in days / 30.4) and in years as (duration in days / 365.25). The total TE exposure duration is the sum over individual participants, and the average TE exposure duration is the total duration divided by the number of participants.

5.3.1.3. At-Risk Exposure Duration

For estimating exposure adjusted incidence rates (EAIR, Section 5.3.4) of treatment-emergent adverse events (TEAEs, Section 5.3.2.3), the at-risk exposure durations of individual participants are required. For a specific TEAE, the at-risk exposure duration in days of a participant is calculated as

- For participants without the specific TEAE: the at-risk exposure duration is the same as the TE exposure duration (Section 5.3.1.2);
- For participants with the specific TEAE: the at-risk exposure duration is calculated as (first onset date of the specific TEAE – study intervention start date + 1).

The at-risk exposure duration in years is calculated as (duration in days / 365.25). The total at-risk exposure duration is the sum over individual participants.

5.3.2. Definition of Endpoints

Definitions of safety endpoints are provided in the sections below.

5.3.2.1. Adverse Event

An Adverse Event (AE) is defined as any term reported by the investigator in the "Adverse Event" eCRF form. The verbatim terms used by the investigators to describe AEs are coded to preferred terms (PT) for classification and tabulation using the latest implemented version of the Medical Dictionary for Regulatory Activities (MedDRA).

5.3.2.2. Serious Adverse Event

An AE is considered serious if the tick box 'Yes' for 'Serious?' is checked on the AE eCRF page. If the information on seriousness is missing, this AE will be considered Treatment-Emergent Adverse Event serious for the analysis.

5.3.2.3. Treatment-Emergent Adverse Event

Treatment-emergent adverse event (TEAE) is any AE occurring at or after the initial administration of study intervention in SOMBRERO through the day of the last dose plus 3 days (see protocol Section 9.4.2).

Note: for participants who entered a post-trial access program or Study NOPRODPAPUH3001 (PLATYPUS), safety information will be reported up to the last dose in SOMBRERO (Section 5.1.6), to avoid duplicate reporting of adverse events (AEs).

5.3.2.4. Adverse Events of Special Interest

AESIs are defined using a selection of PTs (internal MedDRA Query). The full definition is included in Section 6.7.

5.3.2.5. Adverse Events Leading to Death

An AE is considered as leading to death if the tick box "Death" for "Outcome" on the eCRF Adverse Event page is ticked.

5.3.2.6. Deaths

Deaths are derived from the "Death Information" eCRF form. The verbatim terms used by the investigators to describe the death cause are coded to PTs for classification and tabulation using the latest implemented version of MedDRA.

5.3.3. Attributes of Endpoints

- **Primary Trial Objective**: To assess the long-term safety of selexipag in participants who were previously enrolled in an Actelion-sponsored study with selexipag and who derived benefit from selexipag in indications for which a positive benefit-risk has been established.
- **Population**: Safety Set.
- **Study Intervention**: selexipag, tablets for oral administration.
- **Outcome measures:** .
  - TEAEs
  - TEAEs by relationship to study intervention (defined as 'Related' or 'Unrelated' in CRF)
  - TEAEs leading to death (by the tick box 'Death' for 'Outcome' in CRF)
  - TE serious adverse events (SAEs)
  - TE SAEs by relationship to study intervention
  - All SAEs (also including SAEs occurring more than 3 days after the last dose of study intervention, up to EOS)
  - All SAEs by relationship to study intervention
  - TEAEs leading to discontinuation of study intervention
  - TE AESI
  - TEAEs by severity (by 'Maximum intensity' in CRF)
  - Deaths
  - Pregnancies with maternal exposure to selexipag (AE associated with the pregnancies are recorded on the AE/SAE page of the eCRF).
- **Summary method(s) for outcome measures:** In addition to count and percentage for the AEs specified above, EAIR will be presented for TEAEs. Details are specified in Sections 5.3.4 and 5.3.5.

5.3.4. Analysis Methods

The following methods are relevant for analyzing the AEs occurred during the study:

- Frequency of AEs

  AEs reported more than once within a participant (as qualified by the same PT(s)) are counted in the frequency table once.

- Intensity (severity) of AEs

  For AEs reported more than once within a participant (as qualified by the same PT(s)), the worst outcome is considered. The categories of intensity are : mild, moderate, severe, If the intensity is missing, the AE is considered severe. Listings of AEs will include imputed values with a flag to indicate the imputation.

- Relationship to study intervention

Relationship to study intervention is defined as 'related' or 'not related' (see definition in the protocol Section 10.4). For AEs reported more than once for the same participant (as qualified by the same PT(s)), the worst relationship is considered. AEs with missing relationship are considered as related in the analysis. Listings of AEs will include imputed values with a flag to indicate the imputation.

- EAIR of AEs

  For a specific AE (including TEAE), the EAIR per 100 participant-years is calculated as:

  EAIR = 100 × (Number of participants with the specific AE at least once / total at-risk exposure duration).

  The total at-risk exposure duration is defined in Section 5.3.1.3.

Note: AEs continuing from the parent study will not be included in the summaries described above and will be analysed separately (see Section 5.5).

5.3.5. Specifications of Outputs

For each summary table the AEs will be displayed in descending order of incidence either by SOC and then PT within a SOC, or by PT. Summary tables will be provided for the following categories of AEs.

- Overall summary of specified AE categories: A summary table including average TE exposure duration in months as well as count and percentage of participants with at least one occurrence for each of the following AE categories -- TEAE, TEAE related to study intervention, TEAE leading to death, TE SAE, TE SAE related to study intervention, all SAE, all SAE related to study intervention, AE leading to discontinuation of study intervention
- TEAEs: A summary table by SOC and PT; a summary table by PT; a summary table of severe TEAEs by SOC and PT; a summary table of related TEAEs by SOC and PT; a summary table of EAIR by SOC and PT, including also total at-risk exposure duration in years
- TESAEs: A summary table by SOC and PT; a summary table by PT
- TEAEs leading to discontinuation of study intervention: A summary table by SOC and PT
- TEAEs leading to death: A summary table by SOC and PT
- TE AESIs: A summary table by PT, as well as an overview of AESIs leading to discontinuation of study intervention, serious AESIs, related AESIs and AESIs leading to death, total number of recurrent AESIs, total TE exposure duration and average annualized event rate.
- All SAEs up to EOS: A summary table by PT
- TE deaths: A summary table by PT for cause of death
- All deaths up to EOS: A summary table by PT for cause of death.

Listings will be provided for specific participants who:

- Had AEs

- Had SAEs (note: information collected in the eCRF form 'Relevant Medical History' will be provided in the SAEs listing)
- Had AEs leading to premature discontinuation of study intervention
- Had AEs leading to death
- Had died
- Became pregnant (from the AE/SAE form).

The listings will have a flag to indicate TE events.

5.4. Exploratory Endpoints Analyses

5.4.1. Definition of Endpoints

5.4.1.1. Selexipag dose adjustments

Doses and reasons for adjustments are retrieved from the "Study Drug Administration [Selexipag]" eCRF form ('Up-titration', 'Dose adjusted due to use of concomitant medication', 'Dose reduced due to an AE', 'Dose reduced not due to an AE', 'Medication error').

5.4.2. Analysis Methods

The proportion of participants requiring selexipag dose adjustments will be summarized descriptively, by reason. A listing of all dosing records will be provided.

5.5. Other Safety Analyses

In addition to the primary safety analyses described in Section 5.3, the following analyses will also be provided.

5.5.1. Adverse events continuing from the parent study

AEs continuing from the parent study (i.e. with onset date in the parent study that are still ongoing at Day 1 in SOMBRERO) are collected in the "Adverse Event from Parent Study Continuing" eCRF form. A summary table by SOC and PT as well as a listing will be provided.

5.5.2. Adverse events COVID-19 related

COVID-19 related AEs are collected in the "COVID-19 Case of AEs" eCRF form. A summary table by PT on treatment emergent AEs COVID-19 related and a listing of all AEs COVID-19 related will be provided.

5.5.3. Study Intervention Interruptions

A participant is considered to have had a study intervention interruption if the reason for treatment end is either ‘Temporarily interrupted due to an AE’ or ‘Temporarily interrupted not due to an AE’ ("Study Drug Administration " eCRF form). Study intervention interruptions will be derived from the listing of all dosing records as provided in Section 5.4.2.

5.6. Additional Safety Assessments

5.6.1. Clinical Laboratory Tests

No laboratory assessments are performed during the study. Urine (or serum if applicable) pregnancy test for women of childbearing potential will be performed at screening, if not already performed at the last visit of the parent study, and at all study site visits; pregnancy tests will also be performed monthly at home for the months without on-site visits.

The results of the pregnancy tests will not be recorded in the eCRF.

5.6.2. Vital Signs and Physical Examination Findings

Vital signs assessment may be performed for individual participants as clinically indicated but the results of these evaluations will not be recorded in the eCRF.

5.6.3. Electrocardiogram

No reporting of ECG results is planned.

5.7. Interim Analyses

No formal interim analysis is planned. However, data from this study may be used for interactions with health authorities; in such cases details about the ad-hoc interim analyses will be provided in a separate SAP.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	Adverse Events
AESI	Adverse Events of Special Interest
ATC	Anatomic Therapeutic Chemical
DPS	Data Programming Specification
eCRF	Electronic Case Report Form(S)
EOS	End of Study
EOT	End of Treatment
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IMP	Investigational Medicinal Product
IV	Intravenous
IQ range	Interquartile Range
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
NA	Not Available
ND	No Date
NYHA FC	New York Heart Association Functional Classification
OL	Open-label treatment period
OS	Overall Survival
PAH	Pulmonary Arterial Hypertension
PD	Protocol Deviation
PH	Pulmonary Hypertension
PT	Preferred Term
qd	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
SDTM	Standards Consortium Study Data Tabulation Model
SoA	Schedule of Activities
SS	Safety Set
TC	Telephone Call
TEAE	Treatment-Emergent Adverse Event
US	United States
WHO	World Health Organization
WHO FC	World Health Organization Functional Class

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not applicable.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set (Enrolled Set and Safety Set) will be summarized and listed. In addition, the distribution of participants by region, country and site ID will be presented unless otherwise noted.

The following demographic data will be taken from the participant's parent study (or the double-blind core study preceding the parent study) and not recorded in the eCRF of this study:

- Sex,
- Age at IC for SOMBRERO as a continuous variable and in categories (18-25 years, 26-50 years, 51-64 years and >65 years),

  Note: Age at IC for SOMBRERO will be calculated as age at parent study entry plus the time (in years, not rounded) from parent study IC to SOMBRERO IC
- Body weight (kg),
- Height (cm),
- Race (where permitted),
- Ethnicity (where permitted),
- Country,
- Geographical region (Europe, Asia).

Table 3 presents the list of demographic variables that will be summarized for the safety set.

Table 3 - 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)	
Categorical Variables:	
Age (18-25 years, 26-50 years, 51-64 years, and >65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Race[a]	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'.

PH etiology at baseline will be taken from the participant's parent study (or the double-blind core study preceding the parent study) and is not recorded in the eCRF.

Table 4 - Baseline Disease Characteristics Variables

Categorical Variables	
PH etiology	Frequency distribution with the number and percentage of participants in each category.

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations (PDs) may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the ones with major protocol deviations will be summarized by the following categories (DVDECOD).

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other.

Protocol deviations related to COVID-19 will be identified with the text 'COVID-19 related' as a prefix of the PD description.

Protocol deviations are summarized by categories, displaying counts and percentages of participants with at least a major protocol deviation. Summaries will be presented on the Enrolled Set. The summary tables will be sorted by overall frequency, in descending order; if a tie occurs, the tied characteristics will be sorted alphabetically.

All major PDs will also be presented in a listing.

6.5. Appendix 5 Concomitant Medications

All therapies as collected in the "Concomitant Therapy" eCRF form.

The original terms used by the investigators to describe therapies will be coded to PTs for classification and tabulation using the latest version of the WHO Drug code and Anatomic Therapeutic Chemical (ATC) class code dictionaries. The version number will be specified as a footnote in the relevant tables and listings.

Study intervention **concomitant medication** is any treatment that is either ongoing at the start of study intervention or is initiated during the intervention period. It is identifiable in the eCRF page 'Concomitant Therapy' with:

- Start date before intervention start date and end date on or after intervention start date,

  or

- Start date before intervention start date and end date missing with the question 'Is the medication/therapy still ongoing?' answered 'Yes',

  or

- Start date on or after intervention start date and before study intervention end date.

Concomitant medication at SOMBRERO baseline is any medication that is either ongoing at the start of study intervention or is initiated at the start date of study intervention, identified as:

- Start date before or on study intervention start date and end date on or after study intervention start date,

  or

- Start date before intervention start date, end date missing and 'Is the medication/therapy still ongoing?'= **Yes,** ticked by the investigator in the eCRF,

  or

- Start date before or on study intervention start date and end date missing with 'Is the medication/therapy still ongoing?' ≠ **No**'.

PAH-specific medications will be identified by the preferred term according to Table 5 below:

Table 5 - PAH specific medications

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

Counts and percentages of participants having taken at least a concomitant medication will be presented, separately, by Anatomic Therapeutic Chemical (ATC) class and PT within each ATC class as well as by PT. The summary table will present concomitant medications in descending order (e.g., ATC and PT within each ATC with the highest number of occurrences appear first). Equal frequency of different ATC/PTs will be sorted in alphabetical order of the ATC/PT. Participants who took more than once the same concomitant medication (as qualified by the same PT) will be counted only once.

A listing of concomitant medications will be also provided.

Summaries of PAH-specific concomitant medications at baseline and during intervention will be presented by PT and group name. The proportion of participants who received none, 1 and at least 2 PAH-specific concomitant medications at SOMBRERO baseline will be reported.

6.6. Appendix 6 Intervention Compliance

Study intervention compliance will not be assessed in this study.

6.7. Appendix 7 Adverse Events of Special Interest

The following adverse events of special interest will be evaluated 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 separate from other AESIs

AESI are defined in the aesi220.xlsx file available in the statistical computing environment.

6.8. Appendix 8 COVID-19 Medical History

All events as collected in the "COVID-19 Medical History" eCRF form.

The original terms used by the investigators will be assigned preferred terms for classification and tabulation using the latest implemented version of Medical Dictionary for Regulatory Activities (MedDRA).

COVID-19 medical history will be summarized displaying counts and percentages of participants having been diagnosed with at least one COVID-19 related disease. Counts and percentages of participants having been diagnosed with at least one COVID-19 disease are presented by PT. The summary tables are presented in descending order according to the incidence (e.g., PT with the highest number of occurrences appears first). Equal frequency of different PTs is sorted in alphabetical order of the PT. Participants with two or more occurrences of the same disease (as qualified by the same PT) are counted only once.

The COVID-19 medical history will also be reported in a listing.

7. REFERENCES

Coons (2019) Coons, JC, Pogue K, Kolodziej, AR, et al. Pulmonary Arterial Hypertension: a Pharmacotherapeutic Update. Curr Cardiol Rep 2019;21:141.

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