Janssen Research & Development

Statistical Analysis Plan

A Prospective, Multicenter, Single-Arm, Open-Label, Phase 4 Study of the Effect of Selexipag on Right Ventricular Remodeling in Pulmonary Arterial Hypertension Assessed by Cardiac Magnetic Resonance Imaging.

Protocol 67896049PAH4005; Phase 4

JNJ-67896949 (selexipag)

Status:	Approved
Date:	11 April 2023
Prepared by:	Janssen Research & Development, LLC; Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.:	EDMS-RIM-378063, 1.0

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

TABLE OF CONTENTS

TABLE OF CONTENTS **2**

VERSION HISTORY **4**

1. INTRODUCTION **5**
1.1. Objectives and Endpoints 5
1.2. Study Design 7
1.2.1. Analysis Timepoint(s) 9

2. STATISTICAL HYPOTHESES **9**

3. SAMPLE SIZE DETERMINATION **9**

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS **10**

5. STATISTICAL ANALYSES **10**
5.1. General Considerations 10
5.1.1. Visit Windows 10
5.1.2. Study Day and Relative Day 11
5.1.3. Baseline 11
5.1.4. Up-titration period start date 11
5.1.5. Up-titration period end date 11
5.1.6. Maintenance period start date 11
5.1.7. Maintenance period end date 12
5.1.8. Imputation Rules for Missing AE Date/Time of Onset/Resolution 12
5.2. Participant Dispositions 13
5.3. Primary Endpoint(s) Analysis 14
5.3.1. Definition of Endpoint(s) 14
5.3.2. Analysis Methods 15
5.4. Secondary Endpoint(s) Analysis 15
5.4.1. Change from baseline to Week 26 of additional measures of RV function using MRI 15
5.4.2. Change from baseline to Week 26 for 6MWD, WHO FC and NT-proBNP 15
5.4.3. Change from baseline to Week 26 in the number of low-risk criteria 15
5.5. Tertiary/Exploratory Endpoint(s) Analysis 16
5.5.1. Change from baseline to Week 52 on RV function assessed by MRI 16
5.5.2. Change from baseline to Week 26 and Week 52 of RV mass/LV mass 16
5.5.3. Change from baseline to Week 26 of RV function assessed by Echo 16
5.5.4. Change from baseline to Week 26 and Week 52 of LV function assessed by MRI 17
5.5.5. Change from baseline to Week 26 and Week 52 of Right main PA pulsatility assessed by MRI 17
5.5.6. Change from baseline to Week 26 and Week 52 of RV/LV function using 4D flow imaging 17
5.5.7. Impact of individual maintenance dose 17
5.5.8. Change from baseline to Week 52 for 6MWD, WHO FC and NT-proBNP 17
5.5.9. EuroQol 5-dimension scale (EQ-5D-3L) 17
5.5.10. Change from baseline to Week 26 and Week 52 in the difference between the pre-walk and post-walk assessed Borg Dyspnea Index (BDI) 17
5.6. Safety Analyses 17
5.6.1. Extent of Exposure 18
5.6.2. Adverse Events 19
5.6.3. Deaths 20
5.6.4. Additional Safety Assessments 20
5.6.4.1. Clinical Laboratory Tests 20
5.6.4.2. Vital Signs and Physical Examination Findings 21
5.6.4.3. Electrocardiogram 21

5.6.4.4. Other Safety Parameters 21
5.7. Other Analyses 21
5.7.1. Pharmacokinetics 21
5.7.2. Immunogenicity 21
5.7.3. Pharmacodynamics 21
5.7.4. Pharmacokinetic/Pharmacodynamic Relationships 21
5.7.5. Biomarkers 22
5.7.6. Health Economics 22
5.7.7. Other Variables and/or Parameters 22
5.7.8. Definition of Subgroups 22
5.8. Interim Analyses 22
5.8.1. Data Monitoring Committee (DMC) or Other Review Board 22

6. SUPPORTING DOCUMENTATION 23
6.1. Appendix 1 List of Abbreviations 23
6.2. Appendix 2 Changes to Protocol-Planned Analyses 25
6.3. Appendix 3 Demographics and Baseline Characteristics 26
6.4. Appendix 4 Protocol Deviations 27
6.5. Appendix 5 Prior and Concomitant Medications 28
6.6. Appendix 6 Medical History 29
6.7. Appendix 7 Intervention Compliance 30
6.8. Appendix 8 Adverse Events of Special Interest 31
6.9. Appendix 9 Medications of Special Interest 32
6.10. Appendix 10 Laboratory Toxicity Grading 33

7. REFERENCES 34

VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	11-Apr-23	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) presents the planned analysis for the primary endpoint (change from baseline to Week 26 in right ventricular stroke volume (RVSV) assessed by pulmonary artery flow magnetic resonance imaging (MRI)), secondary efficacy endpoints, exploratory efficacy endpoints and safety endpoints.

This SAP is referring to the Global Study Protocol document version 5.0, dated 25 March 2022 [Document number: EDMS-RIM-265483, 5.0].

Following premature study termination, only descriptive statistics will be performed for all collected safety and efficacy data (no inferential statistics).

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effects of selexipag on right ventricular (RV) function in subjects with PAH.	• Change from baseline to Week 26 in RV stroke volume (RVSV) assessed by pulmonary artery flow magnetic resonance imaging (MRI).
Secondary	
• To further assess the effects of selexipag on RV function using MRI.	• Change from baseline to Week 26 assessed by MRI: o RV end-diastolic volume (RVEDV) o RV end-systolic volume (RVESV) o RV ejection fraction (RVEF) o RV mass o RV global longitudinal strain (RVGLS)
• To assess the effects of selexipag on disease severity and exercise capacity.	• Change from baseline to Week 26: o World Health Organization (WHO) Functional Class (FC) o N-terminal-pro-hormone brain natriuretic peptide (NT-proBNP) o 6-minute walk distance (6MWD)
• To evaluate the safety and tolerability of selexipag.	• Treatment-emergent adverse events (AEs) • Serious adverse events (SAEs) • AEs leading to premature discontinuation of study drug • AEs of special interest • Treatment-emergent marked laboratory abnormalities
• To evaluate the effects of selexipag on risk stratification in PAH.	• Change from baseline to Week 26 in number of non-invasive low-risk criteria among the following 8 variables: o Absence of clinical signs of right heart failure o Absence of symptoms progression o Absence of syncope o WHO FC I-II o 6MWD >440 m

	○ NT-proBNP < 300 ng/L ○ Right atrial (RA) area < 18 cm^2, as determined by echocardiography (Echo) ○ Absence of pericardial effusion, as determined by Echo • Change from baseline to Week 26 in number of non-invasive low-risk criteria among the following 3 variables: ○ WHO FC I-II ○ 6MWD >440 m ○ NT-proBNP <300 ng/L
Exploratory	
• To assess the effects of selexipag on RV function using MRI at Week 52	• Change from baseline to Week 52 assess by MRI: ○ RVSV ○ RVEDV ○ RVESV ○ RVEF ○ RV mass ○ RVGLS
• To further assess the effects of selexipag on cardiac morphology.	• Change from baseline to Week 26 and Week 52 assessed by MRI: ○ RV mass/LV mass
• To further assess the effects of selexipag on RV function using Echo.	• Change from baseline to Week 26 assessed by Echo: ○ Tricuspid annular plane systolic excursion ○ Pericardial effusion size scored from 0 to 4 ○ RV end-diastolic area ○ RV end-systolic area ○ RV fractional area change ○ RVSV determined from pulmonary valve Doppler and pulmonary annulus dimension ○ RA area
• To assess the effects of selexipag on left ventricular (LV) function.	• Change from baseline to Week 26 and Week 52 assessed by MRI: ○ LV end-diastolic volume (LVEDV) ○ LV end-systolic volume (LVESV) ○ LV ejection fraction (LVEF) ○ LV mass
• To assess the effects of selexipag on pulmonary artery (PA) function.	• Change from baseline to Week 26 and Week 52 assessed by MRI: ○ Right main PA pulsatility
• To explore 4-dimensional (4D) flow imaging	• In participants from sites able to provide suitable MRI imaging, change from baseline to Week 26 and Week 52 in: ○ RVSV determined from 4D flow imaging in PA

	○ LVSV determined from 4D flow imaging in aorta
• To explore whether individual maintenance dose impacts reverse remodeling.	• Change in RVSV from baseline to Week 26 and Week 52
• To assess the effects of selexipag on disease severity and exercise capacity	• Change from baseline to Week 52: ○ WHO FC ○ NT-proBNP ○ 6MWD
• To explore the effects of selexipag on blood biomarkers.	• Change from baseline to Week 26 and Week 52 in blood biomarkers
• To explore subject's experience.	• EuroQOL 5-dimension scale (EQ-5D-3L) on Day 1, and at Week 26 and Week 52
• To evaluate the effect of selexipag on dyspnea during the 6MWT	• Change from baseline to Week 26 and Week 52 in the difference between the pre-walk and post-walk assess dyspnea Borg Dyspnea Index (BDI)

1.2. Study Design

This is an open-label, multicenter, single-arm, interventional study to assess the effect of selexipag in adult participants (≥18 to <65 years) with a diagnosis of PAH up to 52 weeks on study intervention.

The duration of individual participation will be approximately 60 weeks. The study will be conducted in 3 phases: a 28-day screening phase, a 52-week intervention phase (which will include an initial 12-week up-titration period), and a post-intervention safety follow-up period of at least 30 days. Primary and secondary objectives will be evaluated up to Week 26 and exploratory objectives will be evaluated up to Week 52.

The study comprises the following periods:

- **Screening period:** Informed consent signature marks both the start of the study and the start of the screening period.

  This period serves to assess eligibility (medical history, treatments, blood tests) and to perform baseline efficacy assessments (MRI, Echo, 6MWD, WHO FC, NT-proBNP, and exploratory blood tests). Screening may last up to 28 days. A participant who is temporarily ineligible may be re-screened. Note: in case MRI, Echo, 6MWT or WHO FC assessment was made as part of routine practice in a way that fully complies with the study requirements, and within 28 days before Day 1, these data can be used for the study.

- **Treatment period:** Starts with the first dose of study drug (Day 1 of study) and ends with EOT on the day of the last dose of the study drug which is at Week 52 ± 7 days or at premature discontinuation of study intervention. This period includes:

    - **Day 1:** Day 1 is defined as the day when a participant receives the first dose of study intervention. First dosing should occur at the site. Day 1 may occur once screening assessments are completed, and no later than 28 days after informed consent signature. For re-screened participants, all screening assessments must have been made (or repeated) within 28 days before Day 1.

    - **Up-titration:** During this period, study intervention will be up-titrated from Day 1 to the end of Week 12 (Day 84). Weekly phone calls from the site to participant will be performed to guide the up-titration and collect safety information. At the end of Week 4 (+ 7 days) and Week 12 (+ 7 days) and participants will return to the site for a return/dispensing visit; no assessments will be performed at these site visits.

    - **Maintenance**: During this period, participants will receive study intervention at their individual maintenance dose (IMD) from the start at Week 13 to EOT (scheduled at the end of Week 52, ± 7 days). Monthly phone calls (except when site visits take place) from the site to the participant will be made to monitor participant's safety by collecting information on concomitant medications, AEs and SAEs. At Week 26 (Day 168 to 196), a site visit is scheduled to assess MRI, Echo, 6MWT, WHO FC, blood draw for secondary and exploratory endpoints. At Week 39 (+ 14 days), participants will return to the site for a study drug return/dispensing visit: no assessments will be performed at this site visit.

- **EOT**: EOT should occur at end of Week 52 ± 7 days (Day 350 to 378). At this visit, postbaseline assessments will be performed (MRI, 6MWT, WHO FC, blood draw). In case of premature EOT before Week 16, postbaseline efficacy assessments will be optional and safety assessments will be mandatory. In case of premature EOT after Week 16, all postbaseline assessments will be performed.

- **Safety follow-up:** The safety follow-up will start the day after the last study intervention dose and end with the safety follow-up telephone call (EOS visit).

    - **EOS:** for an individual participant, EOS visit is defined as follows:

      o For participants who complete treatment or who prematurely discontinue study intervention, EOS visit is defined as the safety follow-up telephone call at least 30 days after last dose of study intervention.

      o For participants who complete treatment in the RESTORE study and who are entering another open-label clinical study with selexipag, the EOS visit is defined as the EOT visit.

- **Unscheduled visits:** Unscheduled visits will be allowed and will not be documented in the electronic case report form (eCRF); however, any AE/SAE reported during an unscheduled visit should still be recorded.

Eligible participants will be treated with selexipag for 52 weeks. Dosing with selexipag will start at 200 μg twice daily. On Day 1, the participant will receive only 1 dose, and at each dose change, the first intake of the new dose should be taken in the evening. The site will call the participant once a week from the end of Week 1 to the end of Week 12 and decide whether to increase the dose by 200 μg twice daily if possible. Up-titration will be flexible and can be adapted in case of adverse effects that cannot be relieved with symptomatic treatment. In this case, the site may either postpone up-titration by 1 week or down-titrate study intervention. The dose reached at end of Week 12 will be considered the subject's IMD and will be maintained until EOT.

Efficacy assessments will include MRI, Echo, 6MWD, WHO FC, NT-proBNP, and risk stratification. Safety assessments will include the monitoring of AEs, clinical laboratory evaluations, and pregnancy testing in female participants of childbearing potential. Exploratory assessment will include biomarkers and the participants' experience using a questionnaire.

Imaging will be performed as described in the MRI Image Acquisition Protocol (IAP)/Echo IAP and centrally reviewed. Expert reviewers will be blinded to the participant and timepoint and will assess variables according to the MRI/Echo review charter. For each imaging modality (MRI or Echo), all scans of an individual participant will be reviewed by the same reviewer at the same time, in order to ensure consistent assessment.

1.2.1. Analysis Timepoint(s)

Following premature study termination, there will be only 1 Analysis Timepoint:

- Analysis Timepoint 1 (final analysis all data up to EOS): EOS.

2. STATISTICAL HYPOTHESES

Following premature study termination, there is no formal statistical hypothesis. Only descriptive statistics will be reported.

3. SAMPLE SIZE DETERMINATION

Initial sample size calculation for the primary endpoint was based on the following assumptions:

- A 2-sided Type I error of 5% and a Type II error of 10% (90% power)
- A mean change from baseline to Week 26 in RVSV of +8 mL
- A standard deviation (SD) of 20 mL for the change from baseline to Week 26 in RVSV
- A normal distribution for the change from baseline to Week 26 in RVSV
- 15% of participants with non-valuable RVSV assessment at baseline and/or postbaseline

Based on the above assumptions, a total of 80 participants (68 analyzable + 12 to account for 15% non-evaluable) must be enrolled in order to establish whether change from baseline to Week 26 in RVSV is different from zero (based on paired t-test for single arm).

The assumption that the change from baseline to Week 26 in RVSV is +8 mL is in line with literature suggesting that a difference of 8 mL to 12 mL is clinically relevant[1]. The associated SD of 20 mL is justified by the REPAIR study interim analysis on 42 subjects, where the observed mean change (SD) from baseline to Week 26 was +16.6 mL (16.34).

After the decision to prematurely terminate the study, this sample size calculation was no longer relevant.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis sets are detailed in table 2 below:

Table 2: Overview of the Different Populations for Analyses

Analysis Sets	Description
Screened Analysis Set (SCR)	The screened analysis set (SCR) includes all participants who were screened and received a participant number.
Safety Set (SS)	The safety set (SS) includes all participants from the SCR who received at least 1 dose of study intervention.

Due to premature study termination, only the SCR and the SS will be kept.

5. STATISTICAL ANALYSES

5.1. General Considerations

Following premature study termination, all analyses will be performed using descriptive statistics only. No subgroup analysis will be performed. For efficacy, only listings will be produced. For baseline characteristics and safety, the usual standard tables/listings will be produced.

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 visit windows and the target days for each visit. The reference day is Study Day 1. 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 except for the endpoint. Listed below (Table 3) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 3: Visit Windows

Parameter	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Screening, Efficacy, and Safety	Screening	< 1	[-28 to 1]
Baseline visit	Baseline	<= 1	1
MRI, Echo, 6MWT, WHO FC, Risk stratification	Week 26	113 to 254	180
	Week 52	255 to 400	360
All other parameters	Week 12	2 to 112	84
	Week 26	113 to 210	180
	Week 52	211 to 400	360

*Relative to Study Day 1

5.1.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the day when a participant receives the first dose of study intervention. All efficacy and safety assessments at all visits will be assigned a 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 is defined as the last observation on or before the day of the first dose of study intervention. Participants without a baseline value will be excluded from the corresponding analysis.

5.1.4. Up-titration period start date

It is the first day of selexipag administration. It is derived as the first treatment start date (in chronological order) in the "Study Drug Administration" eCRF.

5.1.5. Up-titration period end date

It is the date of Week 12 visit from the "Medication Kit Dispensation/ Accountability [IWRS or Balance]" eCRF form. In case of premature discontinuation or death prior to Week 12, the 'End of Treatment Date' in the "End of Treatment" eCRF form or the date of death will be considered. If both dates are missing and the subject discontinued from the study prior to Week 12, the 'End of Trial Date' from the "End of Trial" form will be used.

5.1.6. Maintenance period start date

It is derived for subjects who did not discontinue the study prior to Week 12, as the day after the Week 12 visit date.

5.1.7. Maintenance period end date

It is derived for subjects with maintenance period start date available.

It is the 'End of Treatment Date' in the "End of Treatment" eCRF form or the date of death (when applicable). If both dates are missing the 'End of Trial Date' from the "End of Trial" form will be used.

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

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose of study treatment.
  - The day of first dose of study treatment, if the month/year of the onset of AE is the same as month/year of the first dose of study treatment and month/year of the AE resolution date is different
  - The day of first dose of study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose of study treatment date and month/year of the AE resolution date are same.
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first dose of study treatment
  - Month and day of the first dose of study treatment, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the first dose of study treatment,
  - The AE resolution date.
- Completely missing onset dates will not be imputed, but the event will be assumed to be treatment emergent unless otherwise indicated.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

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

Concomitant therapy start dates will be imputed as follows:

- If the start date is missing day only, it will be set to first day of the month.
- If the start date has the year, but is missing the month, it will be set to January 1.
- If the start date is completely missing, it will not be imputed.

Concomitant therapy end dates will be imputed as follows:

- If the start date is missing day only, it will be set to last day of the month.
- If the year is supplied, but is missing the month, it will be set to December 31, or the date of death if this is earlier.
- If the start date is completely missing, it will not be imputed.

For missing or partial assessment dates:

- For scheduled visits, the date will be set to the date closest to the scheduled date, within the range allowed by the partial dates. (For screening assessments, use day -8 as the scheduled date.)
- For unscheduled visits with partial dates:
  - if the day after first dose of study treatment is within the period, it will be set to the day after first dose;
  - otherwise, if the day after first dose of study treatment is within the period, it will be set to the day of first dose;
  - otherwise, if only the day is missing, it will be set to first of the month.

otherwise, if the year is supplied, but is missing the month, it will be set to January 1.

5.2. Participant Dispositions

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication). All screening assessments should then be repeated at the time of re-screening.
If a subject is screened twice and then enrolled, the first screening attempt is not considered in the evaluation of screening failures.
A subject is considered a screening failure as identified from the answer ‘Screen Failure’ to the eCRF question ‘What was the subject's status?’ in the “End of Trial” form and the reason provided in the same form is used as the primary reason for screening failure.

Screened participants and reason for screen failures will be summarized overall.
A subject listing (including the inclusion criteria not met or the exclusion criteria met as collected in the " Inclusion/Exclusion Criteria Not Met" eCRF form) will be also provided for screening failures.

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 (including EOS visit)
- Participants who terminated study prematurely
- Reasons for premature termination of study
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention

A listing will be provided for the following categories:

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

The number of subjects in each analysis set (i.e., SCR, SS) will be summarized.
A listing will be provided displaying the subject membership in the SS. This listing will be run on the SCR.

5.3. Primary Endpoint(s) Analysis

Change in RVSV from baseline to Week 26 will be reported descriptively only (listing).

5.3.1. Definition of Endpoint(s)

The primary endpoint is the change in RVSV from baseline to Week 26 as assessed by pulmonary artery flow MRI:

RVSV at Week 26 - RVSV at baseline

The baseline reference values for RVSV is based on the RVSV as determined from the screening MRI.

Handling of missing data

By design, only one post-baseline RVSV measurement will be taken at the time of the scheduled Week 26 or at the premature EOT visit.

In some instances, the Week 26 (or premature EOT) assessment may be missing with no other post-baseline assessment available.

No imputation methods will be used for the primary endpoint analysis.

5.3.2. Analysis Methods

Due to very limited number of subjects, the absolute values at baseline and post-baseline as well as the absolute changes from baseline to post-baseline in RVSV will be reported in an individual subjects' listing on the SS. No imputation will be performed.

5.4. Secondary Endpoint(s) Analysis

Due to the small sample size, only listings will be provided for all secondary endpoints on the SS. No imputation of missing data will be performed.

5.4.1. Change from baseline to Week 26 of additional measures of RV function using MRI

Change from baseline to Week 26 assessed by MRI for:

- RV end-diastolic volume (RVEDV)
- RV end-systolic volume (RVESV)
- RV ejection fraction (RVEF)
- RV mass
- RV global longitudinal strain (RVGLS).

The change from baseline to Week 26 for these additional measures of RV function assessed by MRI will be listed by timepoint on the SS.

5.4.2. Change from baseline to Week 26 for 6MWD, WHO FC and NT-proBNP

Absolute values as well as the change from baseline to Week 26 in 6MWD will be reported in individual subjects' listing on the SS.

WHO FC will be listed on the SS by timepoint. Changes from baseline in WHO FC will be dichotomized as worsening (i.e., change >0) versus no change or improvement (ie, change ≤0) and reported in the listing.

NT-proBNP will be listed on the SS by timepoint on the SS

5.4.3. Change from baseline to Week 26 in the number of low-risk criteria

The change from baseline to Week 26 in the number of low-risk criteria based on the following 8 variables in accordance with the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension[2]:

- Absence of clinical signs of right heart failure ("Does the patient have clinical signs of right heart failure?" = 'No' in the 'Risk Stratification' eCRF form)
- Absence of symptoms of PAH progression ("Progression of PAH symptoms" = 'No' in the 'Risk Stratification' eCRF form)

- Absence of syncope ("Did the patient experience syncope?" = 'No' in the 'Risk Stratification' eCRF form)
- WHO FC I-II
- 6MWD >440m
- NT-proBNP < 300 ng/L
- Right atrial (RA) area <18 cm^2, as determined by Echo
- Absence of pericardial effusion, as determined by Echo

will be calculated for each participant in the SS, and reported in a listing. The number of low-risk criteria at baseline and Week 26 constitutes the risk score and will be derived for each subject by adding '1' for each of the above criteria met. The number of low-risk criteria for each subject can vary from 0 (worse subjects) to 8 (healthier subjects). Note: the risk score will be assessed excluding subjects with even a single missing value at baseline and/or endpoint visit.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Due to the small sample size, only listings will be provided for all exploratory endpoints.

5.5.1. Change from baseline to Week 52 on RV function assessed by MRI

The absolute values as well as the change from baseline to Week 52 in RVSV, RVEDV, RVESV, RVEF, RV mass and RVGLS assessed by MRI will be listed on the SS.

The number and percent of participants who achieve normalized RVSV at Week 26 and Week 52 will be displayed in the above listing. Patients with a RVSV >60mL will be considered as normal (Kawel-Boehm, 2015)[3], this is consistent with Protocol inclusion criterion 4.2.

5.5.2. Change from baseline to Week 26 and Week 52 of RV mass/LV mass

The absolute values as well as the change from baseline to Week 26 and Week 52 in RV mass/LV mass assessed by MRI will be listed on the SS.

5.5.3. Change from baseline to Week 26 of RV function assessed by Echo

The absolute value as well as the change from baseline to Week 26 of RV function assessed by Echo for the parameters listed below, will be listed on the SS:

- Tricuspid annular plane systolic excursion (TAPSE)
- Pericardial effusion size scored from 0 to 4
- RV end-diastolic area
- RV end-systolic area
- RV fractional area change
- RVSV determined from pulmonary valve Doppler and pulmonary annulus dimension

- RA area.

5.5.4. Change from baseline to Week 26 and Week 52 of LV function assessed by MRI

The absolute values as well as the change from baseline to Week 26 and Week 52 of LVEDV, LVESV, LV ejection fraction and LV mass assessed by MRI will be listed on the SS.

5.5.5. Change from baseline to Week 26 and Week 52 of Right main PA pulsatility assessed by MRI

The absolute values as well as the change from baseline to Week 26 and Week 52 of right main PA pulsatility assessed by MRI will be listed on the SS.

5.5.6. Change from baseline to Week 26 and Week 52 of RV/LV function using 4D flow imaging

The absolute values as well as the change from baseline to Week 26 and Week 52 of RVSV determined from 4D flow imaging in PA and LVSV determined from 4D flow imaging in aorta, in participants from sites able to provide suitable MRI imaging, will be reported in individual subjects' listing on the SS.

5.5.7. Impact of individual maintenance dose

Due to the very limited number of patients, RVSV will not be analyzed by maintenance dose subgroup.

5.5.8. Change from baseline to Week 52 for 6MWD, WHO FC and NT-proBNP

The change from baseline to Week 52 for 6MWD, WHO FC and NT-proBNP will be analyzed similarly as the change from baseline to Week 26 in Section 5.4.2.

5.5.9. EuroQol 5-dimension scale (EQ-5D-3L)

The health profile and health state index score will be derived according to the instrument's instruction for each individual and visit. The absolute values as well as the change from baseline to Week 26 and Week 52 in the health profile, in the health state index score and in the EQ VAS will be reported in a listing on the SS.

5.5.10. Change from baseline to Week 26 and Week 52 in the difference between the pre-walk and post-walk assessed Borg Dyspnea Index (BDI)

The pre-walk assessed BDI and post-walk assessed BDI at Week 26 and Week 52 as well as the difference between the pre-walk and post-walk assessed BDI at both visits and from baseline will be listed on the SS.

5.6. Safety Analyses

All safety analyses will be conducted on the safety analysis set.

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.

5.6.1. Extent of Exposure

Exposure will be summarized up to EOT.

The number and percentage of participants who received study intervention will be summarized.

Descriptive statistics for duration of study intervention (N, mean, SD, median, and range (minimum, maximum)) will be summarized. Participant-years of intervention are calculated as [days of intervention/365.25].

Duration of exposure will be summarized in the following duration categories: <1 week, 1-<4 weeks, 4-<12 weeks, 12-<26 weeks, ≥ 26 weeks.

Cumulative duration of intervention ≥ 1 week, ≥ 4 weeks, ≥ 12 weeks, ≥ 26 weeks will be summarized.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

Total dose days of intervention is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention).

The number (%) of participants with a dose adjustment/dose not administered will be summarized. Reasons for dose adjustments/doses not administered will also be summarized.

Descriptive statistics will be presented for the following parameters during the dose maintenance period:

- The number (%) of participants with a dose adjustment after the 12-week up-titration period. Reasons for dose adjustments will also be summarized.
- Cumulative total dose per participants
- Mean daily dose per participant (after the 12-week up-titration period)
- IMD at end of Week 12 (Day 84).

The mean daily dose of study intervention is calculated as (sum of total daily dose)/study treatment duration.

The total daily dose is calculated according to frequency and dose (μg).

Frequency (coded)[a]	**Total daily dose (µg / day)**
Once a day	dose
Twice a day	2 × dose
Twice weekly	2 × dose / 7
Monthly	dose / 30.5
Every other day	dose / 2
<X> times	<X> × dose
<X> times	<X> × dose / 7
Weekly	dose / 7
Every <X>	dose /(7 × <X>)
Twice per month	2 x dose / 30.5
Missing, other codes	0

a: values coded to CONTINUOUS, ONCE, AS NECESSARY, INFREQUENT, UNKNOWN cannot be used to determine the total daily dose and therefore the total daily dose will be set to zero.

The cumulative total dose per participant is calculated as the sum of total daily dose over the whole treatment period.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 3 days is considered to be treatment-emergent. 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 partial or completely missing, then the event will be considered to be 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 will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Note: for participants who are entering another open-label clinical study with selexipag, safety information will be reported up to the last dose in RESTORE as the EOT visit will be combined with EOS visit. This is intended to avoid duplicate reporting of adverse events (AEs).

Summary tables will be provided for treatment-emergent adverse events by System Organ Class (SOC) and Preferred Term (PT):

- AEs
- Serious AEs (SAEs)

- AEs leading to discontinuation of study intervention
- AEs of COVID-19
- AEs by severity
- AEs by relationship to study intervention

SAEs will also be tabulated up to 30 days after end of study intervention or EOS whichever is first.

In addition to the summary tables, listings will be provided for participants who:

- Had AEs
- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had AEs of special interest (AESI) (see Appendix 8)

5.6.3. Deaths

Deaths will be displayed. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death.
- Relationship to study intervention (yes/no).

A listing of participants who died will be provided.

5.6.4. Additional Safety Assessments

5.6.4.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics (observed values and absolute changes from baseline) will be presented for all chemistry and hematology laboratory tests at scheduled time points. All recorded assessments up to EOT + 3 days will be assigned to the most appropriate visit time point according to the best fitting time window for that assessment.

Scatter plots (eDISH plot) of maximum treatment-emergent ALT and AST versus maximum treatment-emergent total bilirubin up to EOT + 3 days will be presented.

An abnormality (abnormality based on criteria defined in tables in Appendix 10, Section 6.10) will be attributed to the baseline and post baseline values.

Post baseline abnormalities will be compared with their corresponding baseline result:

- Treatment-emergent (TE) will be concluded if the post baseline value is worse than the baseline value.
- If the post baseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low), then the post baseline abnormality will be considered TE. The same applies to the post baseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High).
- If the baseline value is missing, a post baseline abnormality will always be considered as TE.

Treatment-emergent marked laboratory abnormalities (see Section 6.10) will be summarized for each laboratory variable for which marked abnormalities are defined providing their incidence and frequency.

All laboratory data will be listed together with derived marked abnormality flag. A separate listing of all laboratory data for the subjects with at least one marked abnormality value will be provided.

5.6.4.2. Vital Signs and Physical Examination Findings

Physical examination findings will be listed. Vital signs include height (cm), weight (kg), BMI (kg/m2), pulse (beats/min), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg). Observed values and absolute change from baseline will be summarized descriptively by timepoint.

5.6.4.3. Electrocardiogram

Not applicable.

5.6.4.4. Other Safety Parameters

Not applicable.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Not applicable.

5.7.2. Immunogenicity

Not applicable.

5.7.3. Pharmacodynamics

Not applicable.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

5.7.5. Biomarkers

Biomarker samples will be used to generate circulating marker data for computational analyses. These analyses are considered exploratory and the results will be reported separately from the CSR.

5.7.6. Health Economics

Not applicable.

5.7.7. Other Variables and/or Parameters

Not applicable.

5.7.8. Definition of Subgroups

Following study premature termination, no subgroup analysis will be performed.

5.8. Interim Analyses

Not applicable.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

Not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

4D	4-dimensional
6MWD	6-minute walking distance
6MWT	6-minute walking test
AE	adverse event
AESI	adverse event of special interest
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BDI	Borg dyspnea index
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
Echo	Echocardiogram
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQol 5-Dimension scale
FDA	Food and Drug Administration
IAP	image acquisition protocol
ICF	informed consent form
ICH	International Conference on Harmonisation
IMD	individual maintenance dose
IQ	interquartile
LV	left ventricle, left ventricular
LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary arterial pressure
MRI	magnetic resonance imaging
NT-proBNP	N-terminal-pro-hormone brain natriuretic peptide
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PI	principal investigator
PT	prothrombin time
PVR	pulmonary vascular resistance
RA	right atrium, right atrial
RHC	right heart catheterization
RV	right ventricle, right ventricular
RVEDV	right ventricular end diastolic volume
RVEF	right ventricular ejection fraction
RVESV	right ventricular end systolic volume
RVGLS	right ventricular global longitudinal strain
RVSV	right ventricular stroke volume
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure

SD	standard deviation
SMQs	standardised MedDRA queries
SS	Safety set
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

- The number and percent (%) of patients achieving a normalized RVSV assessed by MRI at Week 26 and Week 52 was added as an exploratory endpoint.

- Following premature study termination, it is clarified that only descriptive statistics will be reported, no analysis will be performed using FAS/PP and no subgroup analysis will be performed.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed overall.

Tables 4 and 5 present a list of the demographic variables and baseline disease characteristics that will be summarized overall for the SS analysis set.

Table 4: 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)	
Categorical Variables	
Age (18-<25 years, 25-<51 years, 51-<65 years and >=65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	

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

Table 5: Baseline disease characteristics

Continuous Variables:	**Summary Type**
Time since PAH diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
6MWD (m)	
BDI score (pre-walk, post-walk and difference pre-post)	
NT-proBNP (ng/L)	
Categorical Variables	
PAH Etiology	Frequency distribution with the number and percentage of participants in each category.
WHO FC (II, III)	
Naïve to PH therapies (yes, no)*	

* Naive to PH therapies participants are participants without any of the PAH-specific therapies listed in Section 6.9 (Appendix 9) taken as concomitant at baseline (see Section 6.5 for definition of concomitant medication at baseline)

For each subject time since PAH diagnosis (months) will be derived as:

(Date of Day 1 - date of diagnosis +1) / 30.4375.

Demographics and baseline characteristics will also be listed on the SS.

6.4. Appendix 4 Protocol Deviations

In general, major protocol deviations 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 participants with major protocol deviations will be summarized by category.

See TV-FRM-04718 "Major Protocol Deviation Criteria" for detailed definitions of major protocol deviations.

A specific listing will be provided for major protocol deviations by region and site.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the last available version of World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention.

Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before the first dose of study intervention.

Concomitant medication at baseline is any medication taken at the same day of the first dose of study intervention (see Section 5.1.3).

Summaries of concomitant medications will be presented by ATC class and PT on the SS. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

In addition, **concomitant medications of special interest** (PAH-specific) will be presented on the SS. See Appendix 9 (Section 6.9) for list of medications in PAH-specific category.

In addition, summaries of concomitant medications of special interest at baseline will be presented by ATC class and PT on the SS in the same way.

Prior medications will be summarized by ATC term (highest available level) on the SS.

All prior and concomitant medications will also be listed, with flags for PAH-specific ones and for concomitant at baseline ones.

6.6. Appendix 6 Medical History

Medical history by System Organ Class (SOC) and Preferred Term (PT) will be summarized on the SS. A separate table will be created for Medical history ongoing at baseline ("Is the medical history disease/condition or event still ongoing?" = 'Yes' in the 'General Medical History eCRF form). All Medical history will also be listed.

6.7. Appendix 7 Intervention Compliance

Compliance through EOT will be summarized descriptively, including in the summary the following compliance categorization: < 80%, 80–120% and > 120%.

Compliance will be calculated as follows, for each strength dispensed:

Compliance = [(number of tablets dispensed - number of tablets returned)/2 x total duration of treatment period] x 100.

Compliance will be calculated only if the answer to the question “Was drug accountability performed for returned study treatment?” is ‘Yes’.

Compliance will also be listed.

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 separate from other AESIs

A specific file containing all preferred terms for each category as per last coding version will be maintained.

6.9. Appendix 9 Medications of Special Interest

Concomitant medications of special interest are defined as follows:

Concomitant/Prior Medication Special Interest Category	**Standard ATC Name**	**Note**
PAH-specific medications	Sildenafil	Medications with ATC name containing any of the listed standard ATC names are considered as PAH-specific medications.
PAH-specific medications	Tadalafil	
PAH-specific medications	Vardenafil	
PAH-specific medications	Iloprost	
PAH-specific medications	Epoprostenol	
PAH-specific medications	Beraprost	
PAH-specific medications	Treprostinil	
PAH-specific medications	Selexipag	
PAH-specific medications	Riociguat	
PAH-specific medications	Macitentan	
PAH-specific medications	Bosentan	
PAH-specific medications	Ambrisentan	

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on the tables below.

Blood chemistry marked abnormalities (SI Units)				
Laboratory test name (CDISC Synonym[s])	**LL**	**LLL**	**HH**	**HHH**
Alanine aminotransferase	NA	NA	> 3 × ULN	> 5 × ULN
Aspartate aminotransferase	NA	NA	> 3 × ULN	> 5 × ULN
Alkaline phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Bilirubin; Total bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine	NA	NA	> 1.5 × ULN	> 3 × ULN
Sodium	NA	< 130 mmol/L	> 150 mmol/L	> 155 mmol/L
Potassium	< 3.2 mmol/L	< 3.0 mmol/L	> 5.5 mmol/L	> 6.0 mmol/L

CDISC=Clinical Data Interchange Standards Consortium; NA = not applicable; ULN = upper limit of normal.

Blood chemistry marked abnormalities (SI Units)				
Laboratory test name (CDISC Synonym[s])	**LL**	**LLL**	**HH**	**HHH**
Hemoglobin	< 100 g/L	< 80 g/L	> 20 g/L above baseline	> 40 g/L above baseline
Hematocrit; EVF; PCV (male)	< 0.32 L/L	< 0.20 L/L	> 0.60 L/L	> 0.65 L/L
Hematocrit; EVF; PCV (female)	< 0.28 L/L	< 0.20 L/L	> 0.55 L/L	> 0.65 L/L
Platelets (assuming no platelet cluster)	$< 75 \times 10^9$/L	$< 50 \times 10^9$/L	$> 600 \times 10^9$/L	$> 999 \times 10^9$/L
Leukocytes; white blood cells	$< 3.0 \times 10^9$/L	$< 2.0 \times 10^9$/L	$> 20.0 \times 10^9$/L	$> 100.0 \times 10^9$/L
Neutrophils (Abs)	$< 1.5 \times 10^9$/L	$< 1.0 \times 10^9$/L	NA	NA
Eosinophils (Abs)	NA	NA	$> 5.0 \times 10^9$/L	NA
Lymphocytes (Abs)	$< 0.8 \times 10^9$/L	$< 0.5 \times 10^9$/L	$> 4.0 \times 10^9$/L	$> 20 \times 10^9$/L

CDISC= Clinical Data Interchange Standards Consortium; EVF = erythrocyte volume fraction; NA = not applicable; PCV = packed cell volume.

7. REFERENCES

1. van Wolferen SA, van de Veerdonk MC, Mauritz GJ, Jacobs W, Marcus JT, Marques KMJ, et al. Clinically significant change in stroke volume in pulmonary hypertension. Chest. 2011;139(5):1003-1009.
2. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. doi: 10.1093/eurheartj/ehv317. Epub 2015 Aug 29. PMID: 26320113.
3. Kawel-Boehm N, et al. Normal values for cardiovascular magnetic resonance in adults and children. Journal of Cardiovascular Magnetic Resonance. 2015; 17:29.