Actelion Pharmaceuticals Ltd*
(a Janssen Pharmaceutical Company of Johnson & Johnson)

Clinical Protocol

Protocol Title
A PRospective, Multicenter, Single-arm, Open-label, Phase 4 Study of the Effects of Selexipag on RighT Ventricular RemOdeling in Pulmonary Arterial Hypertension Assessed by Cardiac Magnetic REsonance Imaging (RESTORE)

Selexipag MRI Study

Protocol 67896049PAH4005 (Amendment 3); Phase 4

ACT-293987 / JNJ-67896049 (selexipag)

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United States sites of this study will be conducted under United States Food & Drug Administration Investigational New Drug regulations (21 CFR Part 312).

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Prepared by:	Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-RIM-265483, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	25-Mar-2022
Guidance on Study Conduct During A Natural Disaster/Major Disruption/Pandemic (EDMS-RIM-265584, 4.0)	25-Mar-2022
Amendment 2	08-Jan-2021
COVID-19 Appendix (EDMS-RIM-265584, 3.0)	09-Nov-2020
Amendment 1	20-Feb-2020
Original Protocol	18-Nov-2019

Amendment 3 (25 March 2022)

Overall Rationale for the Amendment: The overall reasons for this protocol amendment are 1) to clarify selected inclusion and exclusion criteria to better define the target population that may benefit from the study intervention and 2) to clarify the definition of end of study (EOS) for the participants continuing selexipag treatment in a continued access program. In addition, small editorial revisions and corrections were made.

A Protocol Amendment Summary of Changes Table for the current amendment is provided below. The updates are indicated in bold text and strikethrough for the deleted text. Changes made in previous protocol amendments are listed in Section 10.10 Appendix 10: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Protocol Title; 1.1 Synopsis	To define the acronym “RESTORE”, the protocol title has been updated with capitalization of relevant letters and without any content change from “A Prospective, Multicenter, Single-Arm, Open-Label, Phase 4 Study of the Effects of Selexipag on Right Ventricular Remodeling in Pulmonary Arterial Hypertension Assessed by Cardiac Magnetic Resonance Imaging (RESTORE)” to “A PRospective, Multicenter, Single arm, Open-label, Phase 4 Study of the Effects of Selexipag on RighT Ventricular RemOdeling in Pulmonary Arterial Hypertension Assessed by Cardiac Magnetic REsonance Imaging (RESTORE)”.	To define the acronym ‘RESTORE’.
1 Protocol Summary (1.1 Synopsis [Exploratory Evaluations]); 4.2 Scientific Rationale for Study Design; 8.3.6 Biomarkers; 10.2. Appendix 2: Clinical Laboratory Tests; Biomarkers)	Clarified the timepoint for exploratory biomarker evaluation by addition of text ‘**at study level**’.	To concise wording to differentiate end of study (EOS) at the study level from EOS at the participant level.

Section Number and Name	Description of Change	Brief Rationale
1 Protocol Summary (1.1 Synopsis [Benefit-risk Assessment])	Added a new section: **BENEFIT-RISK ASSESSMENT** **Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:** • **Efficacy and safety of selexipag have been established in PAH.** • **Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in this protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.** • **Safety will be closely monitored throughout the study.** • **Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:** – **Participants will interrupt or discontinue study intervention for the protocol-allowed reasons.** **It is the investigator's responsibility to monitor the individual risk-benefit ratio of study intervention administration, as well as the degree of distress caused by study procedures at an individual participant level, and to discontinue study intervention or the study if, on balance, investigator believes that continuation would be detrimental to the participants' well-being.**	To align with latest protocol template guidance.
1 Protocol Summary (1.1 Synopsis [Description of Interventions])	Added text: Study intervention: Open-label selexipag **will be provided as round, film-coated tablets for oral administration**.	To align with latest protocol template guidance.
1.2 Schema; 1.3 Schedule of Activities	Added a new footnote: **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. The enrollment in the other open-label clinical study with selexipag must occur on the day of the last visit in the RESTORE study.**	To define EOS=end of treatment (EOT) for participants who enter into an open-label clinical study with selexipag.
1.2. Schema	Updated the Figure 1 Schematic Overview of the Study to indicate that the EOS visit as a phone call instead of a site visit by removal of the symbol for site visit.	To correct an error in the figure aligning it with Table 1.
1.3 Schedule of Activities	Table was updated to include information about '**Target study days'** for all scheduled visits till EOS.	To mark the exact study day for each visit.
1.3 Schedule of Activities (Footnote "l")	Changed the footnote reference "l" for study procedure "Participant's Experience" to "m".	To rectify the error from previous approved version of global protocol amendment.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Footnote "r")	Updated the footnote 'r': In case of **an** epidemic situation **or major disruptions**, eg, COVID-19, the Week 26 visit may be delayed up to an additional 28 days (Week 26 +6/-2 weeks).	For consistency with the information in Appendix 'Guidance on Study Conduct During Natural Disaster/Major Disruption/Pandemic'.
2.1. Study Rationale	Updated the text with addition of a relevant reference: The interim **and final** results of this study have emphasized the relevance of magnetic resonance imaging (MRI) in assessing cardiac changes with PAH treatment.[25,37]	Final results have been published since the last protocol amendment.
4.1 Overall design (Day 1)	Modified the text: First dosing should occur **in the evening of Day 1** ~~at the site~~.	To clarify that the first dose should be taken in the evening to improve tolerability and to obtain an approximate 12-hour dosing interval consistent with twice daily dosing on the following days. Taking the first dose in the evening of Day 1 is in line with the reference label.
4.1. Overall Design (Safety follow-up)	Revised the text: ~~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) at least 30 days after the last dose.~~ – **A safety follow-up period starting on the day after the last dose of study intervention and ends at the End of Study (EOS) visit. 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. The enrollment in the other open-label clinical study with selexipag must occur on the day of the last visit in the RESTORE study. Safety data collection will continue in the other open-label clinical study with selexipag.**	To clarify the EOS definition for participants who completed the study and are continuing selexipag treatment in a continued access program, ie, open-label study.

Section Number and Name	Description of Change	Brief Rationale
4.4. End of Study Definition	Updated the section title from 'EOS Definition' to 'EOS Definition **at Study Level'** Revised the section title from "Study Completion Definition for an Individual Participant" to "**EOS Definition at Participant Level"** and revised the text: ~~The EOS for an individual participant is the end of the safety follow-up, which is planned at least 30 days after last study intervention intake (also applies to participants who prematurely discontinue study intervention). For participants lost to follow-up, the EOS is the last contact with the site. In case of death, death is the EOS.~~ **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.** **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. The enrollment in the other open-label clinical study must occur on the day of the last visit in the RESTORE study. Safety data collection will continue in the other open-label clinical study with selexipag.**	To clarify the EOS definition for participants who completed the study and are continuing selexipag treatment in a continued access program, ie, open-label study.
5.1 Inclusion Criteria; 5.2 Exclusion Criteria	Added weeks and/or days as applicable for relevant eligibility criteria.	For consistency.
5.1 Inclusion Criteria	Revised the inclusion criterion 4: **Diagnosis** of PAH ~~First hemodynamic diagnosis by right heart catheterization (RHC)~~ within ~~12 months~~ **3 years** prior to initiation of selexipag **(Day 1)**, **and most recent right heart catheterization (RHC) within 1 year prior to initiation of selexipag (Day 1)** showing: • mPAP ≥25 mmHg and • PA wedge pressure (PAWP) or LV end-diastolic pressure **(LVEDP)** ≤15 mmHg and • PVR >5 WU (400 dyn.s.cm^{-5}) and • RVSV ≤60 mL as shown in RHC**.** ~~(CO/HR)~~	In clinical practice, the decision of adding selexipag to other pulmonary arterial hypertension (PAH) treatments is often taken at 1 year after initial diagnosis or later. The Steering Committee agreed to expand time from diagnosis to 3 years. The time point of the RHC for assessing eligibility is changed to "most recent" and kept at a maximum of one year prior to selexipag initiation.
5.1 Inclusion Criteria	Modified the inclusion criterion 6 to add alternative units: NT-proBNP ≥300 ng/L **(≥300 pg/mL; ≥35.5 pmol/L)** at screening. Note: If local assessment of BNP (instead of NT-proBNP) is used for eligibility, BNP measurement of ≥50 ng/L **(≥50 pg/mL; 14.4 pmol/L)** will be considered as meeting **the** inclusion criterion.	To provide other common units for N-terminal-pro-hormone brain natriuretic peptide (NT-proBNP) and BNP as local and central laboratories may provide units different from ng/L.

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Revised the text for inclusion criterion 8 for consistency: • Agree to use ~~reliable~~ **acceptable** methods of contraception from Day 1 to at least 30 days after study intervention discontinuation (Section 10.5), and	For consistency with Section 10.5 Appendix 5.
5.2 Exclusion criteria	Revised exclusion criterion 5: Decompensated cardiac failure requiring hospitalization, emergency room visit or intravenous **(iv)** diuretics in the ~~6~~ **10** weeks **(70 days)** before ~~informed consent~~ **Day 1, inclusive**	To clarify that the described conditions are exclusionary not only if present at any time before informed consent signed but also if present at any time during the screening period before or on Day 1.
5.2 Exclusion criteria	Modified exclusion criterion 15: Severe renal impairment (estimated **glomerular filtration rate by Modification of Diet in Renal Disease [MDRD] formula** ~~creatinine clearance~~ ≤30 mL/min/1.73 m^2 or serum creatinine >2.5 mg/dL at screening) or ongoing or planned dialysis.	To correct a discrepancy with Section 10.2 Appendix 2. The value and the units of the assessment remain unchanged.
5.2 Exclusion Criteria	Text added to the footnote c of exclusion criterion 16: **"Absence of hepatic impairment must be documented in the source data as well."**	To document the absence of hepatic impairment in the source data.
5.2 Exclusion criteria	Revised the exclusion criterion 18: Any hospitalization within ~~6~~ **10** weeks **(70 days)** prior to ~~informed consent~~ **Day 1, inclusive** (except elective hospitalizations for surgery or standard monitoring of pre-existing conditions that did not worsen).	To clarify that the described conditions are exclusionary not only if present at any time before informed consent signed but also if present at any time during the screening period before or on Day 1.
5.2 Exclusion criteria	Modified exclusion criteria 20 to add alternative units: Hemoglobin <80 g/L **(<8 g/dL; <4.96 mmol/L)** at screening	To provide other common units for hemoglobin as local and central laboratories may provide units different from g/L.
5.2 Exclusion criteria	Revised exclusion criterion 27 to avoid disambiguation of "any other condition that would interfere with proper cardiac gating": ~~Severe arrythmia, atrial fibrillation, multiple premature ventricular or atrial contractions, or any other condition that would interfere with proper cardiac gating during MRI.~~ • **Cardiac arrythmia assessed severe by the investigator** • **Conditions that could interfere with proper cardiac gating, eg, atrial fibrillation, multiple premature ventricular or atrial contractions.**	To clarify that severe arrhythmia is a contraindication of selexipag, whereas atrial fibrillation, multiple premature ventricular or atrial contractions, and other conditions are excluded because they may interfere with cardiac gating and therefore with cardiac MRI.

Section Number and Name	Description of Change	Brief Rationale
6.6 Concomitant Therapy	Modified a bullet point clarifying forbidden therapies from Day 1 to EOT: • Prostacyclin**,** ~~or~~ prostacyclin analog**, or any other agent acting on the prostacyclin pathway, except iv selexipag in the US for participants who are temporarily (maximum of 14 days; see Section 7.2) unable to take the study intervention orally**	To clarify that participants who received iv selexipag during hospitalization do not need to be discontinued from study intervention.
6.8. Continued Access to Study Intervention After the End of the Treatment Period	Modified the title from "Continued Access to Study Intervention After the End of the Study" to "Continued Access to Study Intervention After the End of the **Treatment Period**" and revised the text under this section to align with the text on continued access program per the transcelerate clinical protocol template: **Local regulations on continued access will always take precedence.** **At the end of their participation in the treatment period, participants who benefit from the study intervention as assessed by the treating physician will be offered the opportunity to continue receiving selexipag via the following options:** • **Switch to commercial selexipag, applicable to participants who reside in a country/territory where selexipag is approved, commercially available and reimbursed for the treatment of participant's PAH.** • **Switch to a PTA program which will be set up for participants who reside in countries/territories where selexipag is not yet commercially available or not reimbursed for the participant's PAH, if allowed as per local regulations.** • **Switch to another open-label clinical study with selexipag, applicable for participants who reside in a country/territory where the conduct of such study is approved by the local health authorities and where the 2 options above are not applicable.** ~~After the participant's study completion, the investigator/delegate will explain to the participant what treatment(s)/medical care is necessary and available according to local regulations. If indicated, the sponsor will provide participants who completed the study (and did not prematurely discontinue study treatment with selexipag) access to selexipag if possible in the participant's country of residence, according to local regulatory requirements, until selexipag can be accessed commercially or through another source in the country where the participant is living, including the option that the participant's physician may~~	To describe the modalities of continued access to selexipag for study participants after end of study treatment period.

Section Number and Name	Description of Change	Brief Rationale
	~~request post-trial access to selexipag from the sponsor, based on favorable benefit/risk ratio for this specific participant, or until the sponsor terminates clinical development of selexipag. If in the best interest of the study participant, commercial selexipag supply should start in the evening of EOT visit (date of last study medication dose) to avoid any unnecessary selexipag treatment interruption.~~	
8. Study Assessments and Procedures, Table 3 (Footnotes 'b' and 'c')	Corrected the key definitions of footnotes 'b' and 'c' as they were mixed up.	To rectify the references to footnotes.
8. Study Assessments and Procedures, Study-specific Materials	Revised the text: • Pregnancy notification form**s** ~~and pregnancy follow-up forms.~~	To indicate that only one form is available.
8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, Serious Adverse Events	Updated the text: Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor **immediately but no later than** within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax) or email. Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.	To align with latest protocol template language.
10.2. Appendix 2: Clinical Laboratory Tests	Added the text: **The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.**	To align with latest protocol template language.
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations; 10.3.1. Regulatory and ethical considerations	Added a new subsection "**Protocol Clarification Communications":** **Protocol Clarification Communications** **If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.** **The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.** **The PCC Documents must NOT be used in place of protocol amendments, but the content of the**	To define the use of protocol clarification communications.

Section Number and Name	Description of Change	Brief Rationale
	PCC Document must be included in any future protocol amendments.	
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations; 10.3.1. Regulatory and ethical considerations, Required Prestudy Documentation	Added the text: **The following documents must be provided to the sponsor before enrollment of the first participant:** • **Completed investigator financial disclosure forms from all subinvestigators** • **Documentation of subinvestigator qualifications (eg, curriculum vitae)** • **Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable** • **Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable**	Revisions made to align with latest protocol template language.
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations; 10.3.4. Data protection	Added text: The informed consent obtained from the participant includes **information about, and where required per applicable regulations**, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This **informed** consent also ~~addresses~~ **provides information to address** the **lawful** transfer of the data to other entities and to other countries/territories. The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete~~.~~, **or make requests concerning his or her personal data in accordance with applicable data protection law**. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations. **In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.**	Revisions made to align with latest protocol template language.

Section Number and Name	Description of Change	Brief Rationale
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations; 10.3.10. Source documents	Added text to the first bullet: • Date of an RHC performed before initiation of selexipag and associated mPAP, CO, **HR,** and either PAWP or LVEDP.	Heart rate (HR) is necessary for the calculation of right ventricular stroke volume (RVSV).
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations; 10.3.10. Source documents	Added a new bullet: • **Documentation confirming absence of hepatic impairment. If known or documented hepatic impairment, all components used for the assessment of Child-Pugh Class should be documented.**	To document the absence of hepatic impairment or assessment of hepatic impairment and its outcome in the source data.
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations; 10.3.14. Study and Site Start and Closure	Revised the text under the subsection "First Act of Recruitment" The first ~~site open~~ **informed consent signed** is considered the first act of recruitment and it becomes the study start date. Updated the title of the subsection from 'Study Termination" to "Study/**Site** Termination".	To align with latest protocol template language.
10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting; 10.4.4. Special Reporting Situations	Added a bullet: • **Reporting of participant pregnancy or participant partner pregnancy**	To align with the requirements in Section 8.5.4 and with the latest protocol template language.
10.5. Appendix 5: Contraceptive and Barrier Guidance	Updated the section heading from "Contraceptive and Barrier Guidance and Collection of Pregnancy Information" to "Contraceptive and Barrier Guidance" and updated the content of the appendix.	To align with latest protocol template language. The collection of pregnancy information is described in Sections 8.5.4 and 10.4.
Guidance on Study Conduct During A Natural Disaster/Major Disruption/Pandemic (EDMS-RIM-265584, 5.0)	Updated the coronavirus disease-2019 (COVID-19) Appendix title and content to include natural disasters and major disruptions, and to anticipate recent developments related to the Covid-19 pandemic including the availability of vaccines.	To provide guidance for conducting the study under special circumstances not only related to COVID-19 but also to natural disasters, major disruptions and pandemics. To align with latest appendix template and to provide guidance on COVID-19 vaccine deployment and its impact on the investigational medicinal product and study procedures.
Throughout the protocol	Updated the terms 'country' and 'countries' to 'country/territory' and 'countries/territories', respectively.	To align with latest protocol template language.

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	• Corrected and updated references, as applicable. • Updated the abbreviations. • Minor corrections, editorial revisions, grammatical, formatting, or spelling changes are made.	For clarity and consistency.

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LIST OF IN-TEXT TABLES AND FIGURES

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1. PROTOCOL SUMMARY

1.1. Synopsis

A PRospective, Multicenter, Single arm, Open-label, Phase 4 Study of the Effects of Selexipag on RighT Ventricular RemOdeling in Pulmonary Arterial Hypertension Assessed by Cardiac Magnetic REsonance Imaging (RESTORE)

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 pulmonary arterial hypertension (PAH) up to 52 weeks on study intervention.

Selexipag is a selective prostacyclin receptor (IP) agonist indicated for the treatment of PAH to delay disease progression and reduce the risk of hospitalization for PAH.

BENEFIT-RISK ASSESSMENT

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- Efficacy and safety of selexipag have been established in PAH.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in this protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study.
- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:

  Participants will interrupt or discontinue study intervention for the protocol-allowed reasons.

It is the investigator's responsibility to monitor the individual risk-benefit ratio of study intervention administration, as well as the degree of distress caused by study procedures at an individual participant level, and to discontinue study intervention or the study if, on balance, investigator believes that continuation would be detrimental to the participants' well-being.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effects of selexipag on right ventricular (RV) function in participants 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: • RV end-diastolic volume (RVEDV) • RV end-systolic volume (RVESV) • RV ejection fraction (RVEF) • RV mass • RV global longitudinal strain (RVGLS)
• To assess the effects of selexipag on disease severity and exercise capacity.	Change from baseline to Week 26: • World Health Organization (WHO) Functional Class (FC)

Objectives	Endpoints
	• N-terminal-pro-hormone brain natriuretic peptide (NT-proBNP) • 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 (AESI) • Treatment-emergent marked laboratory abnormalities
• To evaluate the effects of selexipag on risk stratification in PAH.[10]	Change from baseline to Week 26 in number of non-invasive low-risk criteria among the following 8 variables: • Absence of clinical signs of right heart failure • Absence of symptoms progression • Absence of syncope • WHO FC I–II • 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 assessed 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

Objectives	Endpoints
• 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 further assess the effects of selexipag on disease severity and exercise capacity.	Change from baseline to Week 52: • WHO FC • NT-proBNP • 6-minute walking distance (6MWD)
• To explore the effects of selexipag on blood biomarkers.	Change from baseline to Week 26 and Week 52 in blood biomarkers
• To explore participants' 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 6-minute walking test (6MWT)	• Change from baseline to Week 26 and Week 52 in the difference between the pre-walk and post-walk assessed dyspnea Borg Dyspnea Index (BDI).

Hypothesis

The primary hypothesis of the study is that 26 weeks of selexipag treatment will induce a mean increase in RVSV by 8 mL in participants with PAH.

OVERALL 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 26 and 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 treatment 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.

Efficacy assessments will include MRI, Echo, 6MWT, 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 assessments will include biomarkers, the participants' experience using a questionnaire and efficacy assessments measured at Week 52.

NUMBER OF PARTICIPANTS

The study will enroll approximately 80 participants in total, considering 15% of participants with non-evaluable MRI assessments at baseline and/or Week 26. Thus, it is expected that approximately 68 participants will have evaluable MRIs both at baseline and Week 26. Additionally, it is anticipated that 95 participants will need to be screened in order to enroll 80 participants (assuming 15% screening failure rate).

INTERVENTION GROUP AND DURATION

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 drug. The dose reached at end of Week 12 will be considered the participant's individual maintenance dose (IMD) and will be maintained until EOT.

Description of Interventions

Study intervention: Open-label selexipag will be provided as round, film-coated tablets for oral administration.

Comparator and/or placebo: Not applicable.

EFFICACY EVALUATIONS

- **Imaging**: 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.
- **6MWT**: Tests will follow the sponsor's guidance for 6MWT. Dyspnea will be assessed using the Borg CR 10 Scale® (Section 10.9).
- **WHO FC**: WHO FC will be determined as per WHO definition (Section 10.6).
- **NT-proBNP**: NT-proBNP will be assessed by the central laboratory.
- **Risk stratification**: Clinical signs of right heart failure, progression of PAH symptoms, and syncope will be collected.

SAFETY EVALUATIONS

- **AEs**: AEs will be assessed by sites.
- **Safety laboratory analyses**: Safety laboratory results will be assessed by the central laboratory and will include basic hematology panel, basic clinical chemistry panel, and pregnancy tests for females of childbearing potential. A serum pregnancy test will be performed at the site at screening, at Week 26, and at Week 52 (EOT); urine pregnancy tests will be performed at the site on Day 1 and at the participant's home monthly between Day 1 and End of Study (EOS), except for Month 6 and Month 12, when a serum pregnancy test is performed at the site visit (Weeks 26 and 52).

EXPLORATORY EVALUATIONS

- **Biomarkers**: Exploratory biomarkers will be measured after the end of the study at study level based on the latest scientific evidence regarding RV function and structure at the time of laboratory analysis. No genetic testing of any kind will be performed.
- **EQ-5D-3L questionnaire:** This will be assessed on Day 1, at Week 26, and at Week 52 (Section 10.7).

STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Sample Size Determination

Sample size calculation for the primary endpoint is based on the following assumptions:

- A 2-sided Type I error of 5% and a Type II error of 10% (90% power)
- A 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-evaluable 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 to establish whether change from baseline to Week 26 in RVSV is different from zero (based on paired t-test for single arm).

Populations for Analyses

For purposes of analysis, the following populations are defined:

- **Screened Analysis Set**: The Screened Analysis Set will include all participants who were screened and received a participant number.
- **Safety Set:** The Safety Set (SS) will include all participants from the Screened Analysis Set who received at least 1 dose of study intervention.
- **Full Analysis Set**: The Full Analysis Set (FAS) will include all participants from the SS who had a baseline as well as a postbaseline measurement for RVSV assessed by cardiac MRI from pulmonary artery flow.
- **Per-Protocol Analysis Set:** The Per-Protocol Analysis Set (PPS) will include all participants in the FAS without major protocol deviations that could affect the main analysis of the primary efficacy variable.

Statistical Analyses

General Considerations

The overall Type I error is α=0.05. All analyses will be performed using 2-sided statistical tests.

If the primary endpoint analysis is statistically significant (ie, p-value below nominal alpha), the study will be declared positive.

No multiplicity adjustments will be performed for secondary/exploratory endpoints, and therefore, all associated p-values are of exploratory nature. No interim analysis will be performed.

Participants without a baseline value will be excluded from the corresponding analysis.

Subgroup analyses on primary and secondary endpoints will include WHO FC (II/III) at baseline. Additional subgroup analyses will be specified in the SAP. All subgroup analyses will be of exploratory nature.

Primary Endpoint

The null statistical hypothesis is that the mean change from baseline to Week 26 in RVSV is equal to zero. The alternative statistical hypothesis is that the mean change from baseline to Week 26 in RVSV is different from zero.

The primary efficacy analysis will be performed on the FAS. RVSV will be summarized by timepoint (baseline and Week 26) using descriptive statistics (n, mean, SD, median, Q1 and Q3). The change from baseline to Week 26 in RVSV will be summarized similarly.

Change from baseline in RVSV will be analyzed at α=0.05 (2-sided) using an analysis of covariance (ANCOVA) with a factor for WHO FC (II/III) at baseline and a covariate for baseline RVSV. The mean change from baseline and 95% confidence interval (CI) will be estimated based on the model.

A sensitivity analysis will be performed on the PPS. Another sensitivity analysis will be performed on the SS, where participants with missing postbaseline RVSV will be imputed using their baseline value.

Secondary Endpoints

Change from baseline to Week 26 in RVEDV, RVESV, RVEF, RV mass, RVGLS, 6MWD, and number of low-risk criteria will be summarized descriptively by timepoint and analyzed at α=0.05 (2-sided) on the FAS using an ANCOVA with a factor for WHO FC (II/III) at baseline and a covariate for baseline value. The mean change from baseline and 95% CI will be estimated based on the model.

WHO FC will be summarized on the FAS by timepoint using frequency tables. Changes from baseline in WHO FC will be dichotomized as worsening (ie, change >0) versus no change or improvement (ie, change $\leq$0). Worsening will be analyzed at α=0.05 (2-sided) using a logistic regression model with a factor for WHO FC (II/III) at baseline.

NT-proBNP will be summarized on the FAS by timepoint using descriptive statistics as well as geometric means and coefficients of variation (CVs). The Week 26 versus baseline ratio will be summarized similarly. The ratio versus baseline in NT-proBNP will be log-transformed and analyzed at α=0.05 (2-sided) using an ANCOVA with a factor for WHO FC (II/III) at baseline and a covariate for baseline log NT-proBNP.

All analyses for secondary endpoints are of exploratory nature because there will be no adjustment for multiplicity. Additional analyses will be performed on the SS for all secondary endpoints, where participants with missing postbaseline values will be imputed using their baseline values.

Exploratory Endpoints

Exploratory variables will be analyzed at α=0.05 (2-sided) on the FAS and SS. Details will be specified in the SAP.

Biomarker exploratory analyses will be specified in a separate specific SAP.

Safety Analyses

Safety analyses will be performed on the SS.

Adverse Events

A treatment-emergent AE is any AE from first dose up to 3 days after end of study intervention. The number and percentage of participants experiencing at least 1 treatment-emergent AE or SAE will be tabulated by:

- Medical Dictionary for Regulatory Activities system organ class and individual preferred term, in descending order of incidence.
- Frequency of participants with events coded with the same preferred term, in descending order of incidence.

Treatment-emergent AEs and SAEs will be tabulated as described above by severity and relationship to study intervention. SAEs will be also tabulated up to 30 days after end of study intervention.

AEs leading to premature discontinuation of study intervention, AEs with an outcome of death, and AEs of special interest will be summarized as described above. The detailed list of AEs of special interest will be specified in the SAP.

AEs occurring during titration period will also be summarized separately.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study intervention, and for AEs with an outcome of death.

The following AEs will be listed only:

- AEs occurring prior to first study intervention dose
- Non-serious AEs occurring after EOT + 3 days
- SAEs occurring more than 30 days after discontinuation of study intervention

Clinical Laboratory Tests

Descriptive summary statistics by visit will be provided for observed values and absolute changes from baseline, in both hematology and clinical chemistry laboratory tests. In order to minimize missing data and to allow for out-of-window visits, all recorded assessments up to EOT + 3 days will be assigned to the most appropriate visit timepoint according to the best fitting time window for that assessment.

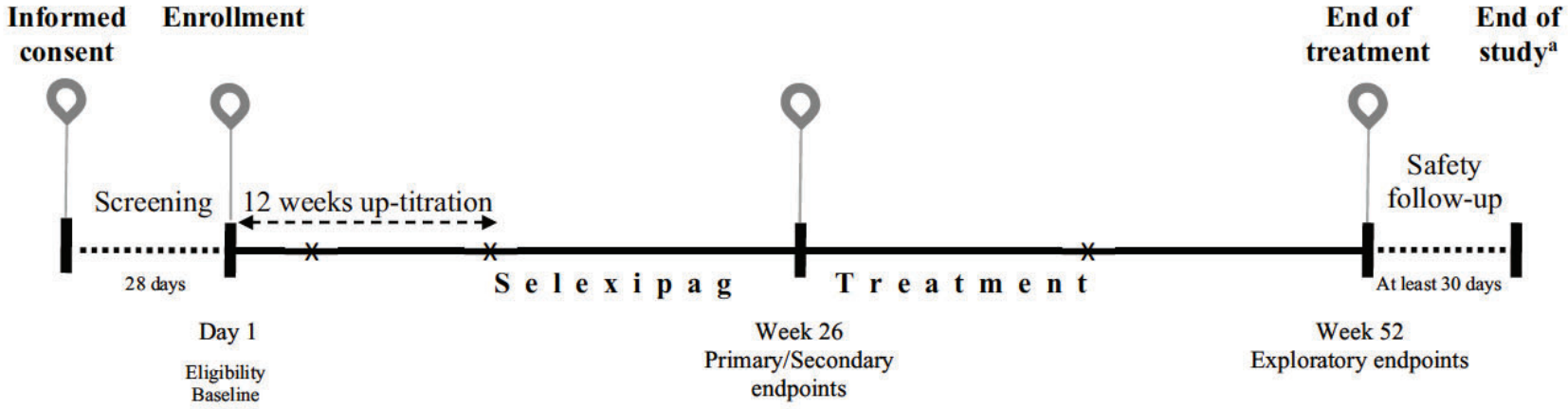
The sponsor's internal guidelines will be used for the definitions of marked abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables will be transformed to standard units. All laboratory data transferred will be taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

Marked laboratory abnormalities will be summarized for each laboratory variable providing the incidence and frequency. Absolute values and changes from baseline of laboratory values during the course of the study will also be summarized.

The number and percentage of participants with treatment-emergent laboratory abnormalities will be tabulated.

1.2. Schema

Figure 1: Schematic Overview of the Study



EOS End of Study; EOT End of Treatment

[a] 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. The enrollment in the other open label clinical study with selexipag must occur on the day of the last visit in the RESTORE study.

1.3. Schedule of Activities

Table 1: Schedule of Activities

PERIODS	SCREENING	SELEXIPAG TREATMENT							FOLLOW-UP
		Up-titration to IMD (Day 1 to Week 12)[a]			Maintenance with IMD (Weeks 13 to 52)				
Visit name	Screening	Treatment initiation	Phone calls #1 to #12	Study drug dispense/return #1 and #2	Phone calls #13 to #19	Primary efficacy assessments[p]	Study drug dispense/return #3	EOT	EOS[s] (Phone call #20)
Time phase	Day −28 to Day 1	Day 1	Weekly (± 3 days)	Week 4 (+7 days) and Week 12 (+7 days)	Monthly[q] (± 5 days)	Week 26 (±14 days[b,r])	Week 39 (± 14 days)	Week 52 ± 7 days or at premature EOT[b]	At least 30 days after EOT
Target study days / Study procedure		1	7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84	28, 84	120, 150, 210, 240, 270, 300, 330	180	270	360	390
Screening/Administrative									
Informed consent[c]	X								
Inclusion/exclusion criteria[d,o]	X								
Demographics, PAH characteristics	X								
Medical history	X								
Concomitant medication	X	X	X		X	X		X	X
Contraceptive methods[e]	X	X	X		X	X		X	X
Pregnancy test[e]	X[f]	X[g]	Monthly[h]		X	X[f]		X[f]	X[h,i]
Study Intervention Administration									
Dispense/administer study drug		X		X		X	X		
Return study drug				X		X	X	X	
Study drug accountability				X		X	X	X	
Efficacy Evaluations									
MRI	X[j]					X[k]		X	

PERIODS	SCREENING	SELEXIPAG TREATMENT							FOLLOW-UP
		Up-titration to IMD (Day 1 to Week 12)[a]			Maintenance with IMD (Weeks 13 to 52)				
Visit name	**Screening**	**Treatment initiation**	**Phone calls #1 to #12**	**Study drug dispense/return #1 and #2**	**Phone calls #13 to #19**	**Primary efficacy assessments[p]**	**Study drug dispense/return #3**	**EOT**	**EOS[s] (Phone call #20)**
Time phase	**Day −28 to Day 1**	**Day 1**	**Weekly (± 3 days)**	**Week 4 (+7 days) and Week 12 (+7 days)**	**Monthly[q] (± 5 days)**	**Week 26 (±14 days[b,r])**	**Week 39 (± 14 days)**	**Week 52 ± 7 days or at premature EOT[b]**	**At least 30 days after EOT**
Target study days / Study procedure		**1**	**7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84**	**28, 84**	**120, 150, 210, 240, 270, 300, 330**	**180**	**270**	**360**	**390**
Echo	X[j]					X[k]			
6MWT including Borg CR 10®	X[j]					X[k]		X	
WHO FC	X[j]					X[k]		X	
Risk stratification	X					X[k]			
Safety Evaluations									
Vital signs (BP, HR, weight)	X	X				X		X	
Participant's experience[m]		X				X		X	
Physical examination	X					X[l]		X	
Blood draw[n]	X					X		X	
AEs and SAEs	X	X	X		X	X		X	X

6MWT=6-minute walking test; AE=adverse event; Echo=echocardiography; EOS=End of Study; EOT=End of Treatment; IMD=individual maintenance dose; MRI=magnetic resonance imaging; NT-proBNP= N-terminal-pro-hormone brain natriuretic peptide; PAH=pulmonary arterial hypertension; SAE=serious adverse event; WHO FC=World Health Organization functional class

Footnotes:

a. In principle, the maintenance dose can be reached after 8 weeks. Additional time is given to allow slower up-titration.
b. Participants must NOT take the morning study intervention dose before any visit-related procedure.
c. Must be signed before first study-related activity.
d. For eligibility criteria based on blood laboratory results, the decision to enroll a participant can be made on the basis of local laboratory results obtained during screening; however, the blood samples must still be sent to the central laboratory for analysis.
e. For females of childbearing potential (Section 10.5).
f. Serum pregnancy test.

g. Urine pregnancy test at site.
h. Urine pregnancy test at participant's home. The site will call female participants of childbearing potential monthly to check the pregnancy test result. A window of ±5 days for each pregnancy test/phone call will be allowed.
i. Test to be done within 30 to 37 days after EOT.
j. If MRI, Echo, 6MWT, or WHO FC assessments were done 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.
k. Optional in case of premature EOT before end of Week 16 (Day 112).
l. Only if EOT.
m. Participant's experience refers to the EQ-5D-3L questionnaire (Section 10.7).
n. For safety laboratory analyses (Section 8.4.2), NT-proBNP and biomarkers (Section 8.3.6).
o. If the results for the screening blood samples from the central laboratory are not available in time for Day 1 visit, an additional blood sample may be drawn to verify eligibility based on a local laboratory test.
p. Including premature EOT. In case of premature EOT, the EOT visit should take place within 7 days after the decision to end study intervention.
q. Except for month of Week 26 and Week 52.
r. In case of an epidemic situation or major disruptions, eg, COVID-19, the Week 26 visit may be delayed up to an additional 28 days (Week 26 +6/-2 weeks).
s. 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. The enrollment in the other open-label clinical study with selexipag must occur on the day of the last visit in the RESTORE study.

2. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a serious chronic disorder of the pulmonary circulation, a syndrome of diverse etiology and pathogenesis characterized by a progressive increase in pulmonary arterial pressure (PAP) and in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death.[3,17,19]

PAH is associated with structural changes in both pulmonary vasculature and right ventricle (RV). The changes in vascular structure involve 3 combined elements: vasoconstriction, vascular-wall remodeling, and thrombosis *in situ*.[14] The changes in the RV mainly consist of hypertrophy, dilation, altered contractility, and septal bowing.[9,22,36] Collectively, these changes of the RV are termed remodeling.

PAH is hemodynamically defined as a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg with normal pulmonary artery wedge pressure or left atrial pressure (≤15 mmHg) and a PVR greater than 3 Wood units (WU).[10,13]

The updated clinical classification of pulmonary hypertension classifies the numerous conditions that are known to lead or be associated with the development of PAH into 4 groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause (idiopathic), in a familial setting (heritable), as the result of the use of drugs and toxins, or it can be associated with a connective tissue disease, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease, or schistosomiasis.[26,27]

Selexipag (JNJ-67896049 [also known as ACT-293987]) is a selective, orally available, long-acting, non-prostanoid agonist of the prostacyclin receptor (IP receptor), approved and commercially available for the treatment of patients with PAH in the United States, the European Union, Japan, and other countries/territories. Selexipag is currently under development for sarcoidosis-associated pulmonary hypertension, chronic thromboembolic pulmonary hypertension, arteriosclerosis obliterans with intermittent claudication, and lumbar spinal stenosis with intermittent claudication.

Throughout the protocol, the term “study intervention” refers to study drug.

The term “sponsor”, used throughout this document, refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

Selexipag was approved on the basis of long-term clinical efficacy; however, short-term cardiac imaging data on selexipag are lacking.[28]

In PAH, RV function is a determinant of survival. In order to compensate for the increased PVR, the RV remodels. It dilates and hypertrophies, but may be unable to maintain a sufficient cardiac

output. The AC-055-403 REPAIR study[a] evaluated the effect of macitentan, an endothelin receptor antagonist (ERA), on the right ventricle. The interim and final results of this study have emphasized the relevance of magnetic resonance imaging (MRI) in assessing cardiac changes with PAH treatment.[25,37] The study has shown that RV reverse remodeling can be detected, as the RV re-shapes to return closer to a healthy heart. Furthermore, an increase in RV stroke volume (RVSV) by 8 mL to 12 mL is considered clinically significant.[35]

2.2. Background

For the most recent comprehensive quality, nonclinical, and clinical information regarding selexipag, see the latest version of the Investigator's Brochure.[16]

2.3. Benefit-Risk Assessment

2.3.1. Known Benefits

Efficacy of selexipag in the treatment of adult participants with symptomatic PAH was demonstrated in study AC-065A302 (GRIPHON), the largest (N 1156) and only randomized long-term (mean duration 1.5 years and up to 4.2 years), controlled morbidity/mortality study conducted with an IP-receptor agonist.[18,28] A highly statistically significant effect on the primary endpoint, risk of first morbidity or mortality event during treatment, was observed: the hazard ratio versus placebo was 0.60 (99% confidence interval [CI]: 0.46, 0.78, 1-sided unstratified log-rank p <0.0001), corresponding to a 40% relative risk reduction versus placebo. The treatment effect was consistent across World Health Organization (WHO) functional class (FC) II III and was fully preserved in participants already treated with at least 1 approved PAH-specific medicine at baseline (80% of the study population), as well as in participants treated with 2 such medicines (30% of the study population). In all analyses, the effect of selexipag was established early and was sustained over this long-term study. GRIPHON was the first study to demonstrate the long-term outcome benefit of an oral IP-receptor agonist, in particular when added sequentially to therapies acting on other pathogenic pathways in PAH (endothelin and nitric oxide pathways). The study outcome is reflected in the current consensus guidelines for PAH, where selexipag is the only IP-receptor agonist with a Class I evidence recommendation for sequential drug combination therapy.[10]

2.3.2. Known and Potential Risks

The short and long-term safety profile of selexipag has been established in PAH participants in study AC-065A302 (GRIPHON), conducted in 1156 participants, and is mainly characterized by prostacyclin-associated adverse events (AEs) linked with the mode of action of selexipag. Such AEs typically occur during the initial phase of individualized dose titration, and the susceptibility varies between individuals. Adverse drug reactions reflecting the mode of action of selexipag included: headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing.

[a] NCT02310672; EUDRACT: 2014-004066-20

Other AEs reported more frequently in the selexipag group compared with placebo group included hypotension, anemia, hyperthyroidism, nasopharyngitis, nasal congestion, decreased appetite, weight decreased, rash, urticaria, and erythema.

Hypotension was reported more frequently in the selexipag group than in the placebo group (5.0% and 3.1%, respectively). In the selexipag group, 9.7% of participants had systolic blood pressure (SBP) <90 mmHg on at least 1 occasion, compared with 6.7% in the placebo group. A decrease from baseline of >40 mmHg in SBP was reported for 2.3% and 3.0% of participants in the selexipag and placebo groups, respectively.

Hyperthyroidism was reported more frequently in the selexipag group compared with the placebo group. Corresponding laboratory changes were a small reduction in thyroid-stimulating hormone at most postbaseline visits.

Anemia was reported more frequently in the selexipag group, and a small reduction in hemoglobin was observed at most postbaseline visits.

2.3.3. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- Efficacy and safety of selexipag have been established in PAH.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5.1 and Section 5.2, respectively) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study.
- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:

  Participants will interrupt or discontinue study intervention for the reasons included in Sections 7.2 and 7.1, respectively.

It is the investigator's responsibility to monitor the individual risk-benefit ratio of study intervention administration, as well as the degree of distress caused by study procedures at an individual participant level, and to discontinue study intervention or the study if, on balance, investigator believes that continuation would be detrimental to the participants' well-being.

More detailed information about the known and expected benefits and risks of selexipag is available in the Investigator's Brochure.[16]

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effects of selexipag on RV function in participants with PAH.	Change from baseline to Week 26 in RV stroke volume (RVSV) assessed by pulmonary artery flow MRI.
Secondary	
• To further assess the effects of selexipag on RV function using MRI.	Change from baseline to Week 26 assessed by MRI: • RV end-diastolic volume (RVEDV) • RV end-systolic volume (RVESV) • RV ejection fraction (RVEF) • RV mass • RV global longitudinal strain (RVGLS)
• To assess the effects of selexipag on disease severity and exercise capacity.	Change from baseline to Week 26: • WHO FC • N-terminal-pro-hormone brain natriuretic peptide (NT-proBNP) • 6-minute walk distance (6MWD)
• To evaluate the safety and tolerability of selexipag.	• Treatment-emergent 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.[10]	Change from baseline to Week 26 in number of non-invasive low-risk criteria among the following 8 variables: • Absence of clinical signs of right heart failure • Absence of symptoms progression • Absence of syncope • WHO FC I–II • 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 assessed by MRI: • RVSV • RVEDV • RVESV

Objectives	Endpoints
	• 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 participants' 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 assessed dyspnea Borg Dyspnea Index (BDI).

HYPOTHESIS

The primary hypothesis of the study is that treatment with selexipag for 26 weeks will induce a mean increase in RVSV by 8 mL in participants with PAH.

4. STUDY DESIGN

4.1. Overall 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. Following are detailed descriptions of the study 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 rescreened once (Section 5.4). Note: if MRI, Echo, 6MWT, or WHO FC assessments were done 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 study drug which is at Week 52 ± 7 days or at premature discontinuation of study intervention.

  Day 1: Day 1 is defined as the day when a participant receives the first dose of study intervention. First dosing should occur in the evening of Day 1. Day 1 may occur once screening assessments are completed, and no later than 28 days after informed consent signature. For rescreened participants, all screening assessments must have been made within 28 days before Day 1; only screening assessments beyond the 28-day window will need to be repeated. The last study procedure to be performed on Day 1 will be selexipag intake.

  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 visits.

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: A safety follow-up period starting on the day after the last dose of study intervention and ends at the End of Study (EOS) visit. For an individual participant, EOS visit is defined as follows:

- 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.
- 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. The enrollment in the other open-label clinical study with selexipag must occur on the day of the last visit in the RESTORE study. Safety data collection will continue in the other open-label clinical study with selexipag.

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 participant's IMD and will be maintained until EOT.

Efficacy assessments will include MRI, Echo, 6MWT, 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.

A diagram of the study design is provided in Figure 1.

4.2. Scientific Rationale for Study Design

The primary cause of death in PAH is right ventricular failure. Several studies have shown that RV function has a prognostic relevance in this condition.[12,29,32,34] Cardiac MRI is a safe, non-invasive method to assess RV geometry and function, with low between-study[6,11] and between-observer[6] variability. In addition, cardiac imaging can be satisfactorily assessed without contrast medium. Therefore, it is the method of choice for assessing RV remodeling.

Non-controlled, open-label trials are classically used in imaging studies that assess cardiac changes in PAH.[4,12,20,24,33,38] Open-label trials have a potential for bias. Bias in the assessment of imaging, including the primary endpoint, is reduced by ensuring objectivity of assessment.

Objectivity of imaging results is ensured by central assessment of images by assessors who are blinded to the participant and imaging timepoint (ie, before or during treatment). Because PAH is a progressive disease, reverse remodeling is not expected to be observed unless it is induced by a study intervention. Therefore, participants may be used as their own control (ie, a participant's postbaseline values may be compared with the corresponding baseline values).

The primary endpoint will be assessed at 26 weeks as this is a sufficient study intervention duration to enable a relevant change and also early enough to have a relatively low proportion of participants dropping out for the primary endpoint.

This study will contain a 12-week up-titration period. The goal of the up-titration is to ensure that each participant reaches his/her individual highest tolerated dose; ie, without unmanageable prostacyclin-associated adverse effects. Based on the GRIPHON study, the effect of selexipag on the composite endpoint of death from any cause or a complication related to PAH is consistent across different IMDs following up-titration.

It is hypothesized that selexipag may have a beneficial effect on circulating biomarkers involved in RV function and structure. Therefore, changes in such biomarkers from baseline to Week 26 and Week 52 will be explored. Biomarkers will be measured after the EOS at study level and will be based on the latest scientific evidence regarding RV function and structure at the time of laboratory analysis. No genetic testing of any kind will be performed.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. It will be explained that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is that PAH therapy escalation might be delayed in some participants due to study participation. This is mitigated by assessing the primary endpoint after a relatively short study duration and the permission to escalate PAH therapy at any time.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.[1]

4.3. Justification for Dose

Study intervention will be up-titrated (see Section 6.1) to allow each participant to reach the IMD, in the range of 200 to 1,600 µg twice daily. This is in accordance with the approved regimen and doses as per the summary of product characteristics and United States prescribing information for UPTRAVI®.[30,31] Depending on the dose, a single dose of study intervention may consist of 1 or more tablets.

4.4. End of Study Definition

EOS Definition at Study Level

The EOS is defined as the day of the last study assessment shown in the schedule of activities (Table 1) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the clinical trial agreement.

EOS Definition at Participant Level

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.

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. The enrollment in the other open-label clinical study with selexipag must occur on the day of the last visit in the RESTORE study. Safety data collection will continue in the other open-label clinical study with selexipag.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of the study intervention. See Section 5.4 for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in Section 10.3.

Eligibility assessment may be made on the basis of local laboratory results assessed during screening, in order to permit a quick decision and reduce participant burden. The local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF. Screening blood samples are nevertheless required to be sent to the central laboratory.

For a discussion of the statistical considerations of participant selection, see Section 9.2.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Signed informed consent prior to any study-mandated procedure.

2. Criterion modified per Amendment 2
   2.1 WHO FC II or III. Enrollment will be stratified by WHO FC II or III. Proportion of participants with WHO FC II and WHO FC III are expected to be approximately 40% and 60%, respectively.

3. Criterion modified per Amendment 2
   3.1 PAH etiology belonging to one of the following groups according to classification[27]:
   - Idiopathic PAH
   - Heritable PAH
   - Drugs or toxins induced
   - PAH associated with connective tissue disease
   - PAH associated with congenital heart disease, with simple systemic-to-pulmonary shunt at least 1 year after surgical repair.

4. Criterion modified per Amendment 2
   4.1 Criterion modified per Amendment 3
   4.2 Diagnosis of PAH within 3 years prior to initiation of selexipag (Day 1), and most recent right heart catheterization (RHC) within 1 year prior to initiation of selexipag (Day 1) showing:
   - mPAP ≥25 mmHg and
   - PA wedge pressure (PAWP) or LV end-diastolic pressure (LVEDP) ≤15 mmHg and
   - PVR >5 WU (400 dyn.s.cm ^{5}) and
   - RVSV ≤60 mL as shown in RHC.

5. Criterion modified per Amendment 2
   5.1 Patients already receiving PAH-specific oral mono or dual therapy (ie, phosphodiesterase type 5 inhibitors (PDE-5i) or soluble guanylate cyclase stimulators (sGCs) and/or ERA) or patients who are not candidates for these therapies. If on oral PAH-specific therapy, treatment has to be stable (ie, no introduction of new therapies or changes in dose) for at least 90 days prior to both ICF signature and Day 1.

6. Criterion modified per Amendment 2
   6.1 Criterion modified per Amendment 3
   6.2 NT-proBNP ≥300 ng/L (≥300 pg/mL; ≥35.5 pmol/L) at screening. Note: If local assessment of BNP (instead of NT-proBNP) is used for eligibility, BNP measurement of ≥50 ng/L (≥50 pg/mL; 14.4 pmol/L) will be considered as meeting the inclusion criterion.

7. Criterion modified per Amendment 2

7.1 Men or women ≥18 years (or the legal age of consent in the jurisdiction in which the study is taking place if greater than 18) and <65 years.

8. Criterion modified per Amendment 2
   8.1 Criterion modified per Amendment 3
   8.2 Women of childbearing potential (Section 10.5) must meet the following criteria:
   - Have a negative serum pregnancy test during screening and a negative urine pregnancy test on Day 1, and
   - Agree to use acceptable methods of contraception from Day 1 to at least 30 days after study intervention discontinuation (Section 10.5), and
   - If only using hormonal contraception, have used it for at least 1 month (30 days) before Day 1, and
   - Agree to perform monthly pregnancy tests to at least 30 days after study intervention discontinuation.

9. New criterion per Amendment 2
   9.1 6MWD ≥150 m during screening period.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Prior use of IP-receptor agonist, prostacyclin, or prostacyclin analog. Use of such treatments for vasoreactivity testing is not exclusionary; intermittent use of such treatments for digital ulcers or Raynaud's phenomenon is not exclusionary if stopped >6 months (180 days) prior to Day 1.

2. Treatment with strong inhibitors of CYP2C8 (eg, gemfibrozil) within 4 weeks (28 days) prior to Day 1.

3. Treatment with another investigational drug planned or taken within 12 weeks (84 days) prior to Day 1.

4. Cardiopulmonary rehabilitation programs based on exercise between informed consent and expected Week 26 visit date.

5. Criterion modified per Amendment 3
   5.1 Decompensated cardiac failure requiring hospitalization, emergency room visit or intravenous (iv) diuretics in the 10 weeks (70 days) before Day 1, inclusive.

6. Severe coronary heart disease or unstable angina.

7. Cerebrovascular events (eg, transient ischemic attack, stroke) within 3 months (90 days) prior to Day 1.

8. Left atrial volume indexed for body surface area ≥43 mL/m^2, assessed by Echo or cardiac MRI.

9. Myocardial infarction within 6 months (180 days) prior to Day 1.

10. Criterion modified per Amendment 2
10.1 Body mass index >40 kg/m^2 or body weight <40 kg.

11. Criterion modified per Amendment 2
11.1 Presence of one or more of the following signs of relevant lung disease at any time up to Day 1 - **if pulmonary function test results are missing, then exclusion 11 is considered as met.**
    - Diffusing capacity of the lung for carbon monoxide <40% of predicted UNLESS computed tomography reveals no or mild interstitial lung disease
    - Forced vital capacity <60% of predicted[b]
    - Forced expiratory volume in 1 second <60% of predicted[b].

12. Known or suspected pulmonary veno-occlusive disease (PVOD).

13. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

14. SBP <90 mmHg at screening or on Day 1.

15. Criterion modified per Amendment 3
15.1 Severe renal impairment (estimated glomerular filtration rate by Modification of Diet in Renal Disease [MDRD] formula ≤30 mL/min/1.73 m^2 or serum creatinine >2.5 mg/dL at screening) or ongoing or planned dialysis.

16. Criterion modified per Amendment 2
16.1 Criterion modified per Amendment 3
16.2 Known and documented severe hepatic impairment (with or without cirrhosis) at screening, defined as Child-Pugh Class C[c].

17. Known or suspected uncontrolled thyroid disease (hypo- or hyperthyroidism).

18. Criterion modified per Amendment 3
18.1 Any hospitalization within 10 weeks (70 days) prior to Day 1, inclusive (except elective hospitalizations for surgery or standard monitoring of pre-existing conditions that did not worsen).

[b] Pulmonary function tests may be performed either with or without the use of bronchodilators, as per local clinical practice.

[c] The assessment of hepatic impairment (Child-Pugh Score) must be fully documented for participants who have clinical signs and/or evidence (from central and/or local lab) of hepatic impairment. Absence of hepatic impairment must be documented in the source data as well.

19. Concomitant life-threatening disease with a life expectancy of less than 12 months.

20. Criterion modified per Amendment 3
20.1 Hemoglobin <80 g/L (<8 g/dL; <4.96 mmol/L) at screening.

21. Hypersensitivity to selexipag or any study intervention excipient (mannitol, maize starch, hydroxypropylcellulose, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, carnauba wax, iron oxide red, iron oxide yellow, iron oxide black).

22. Criterion modified per Amendment 2
22.1 Pregnancy, breastfeeding, or intention to become pregnant during the study.

23. Any factor or condition likely to affect compliance with study intervention or visit plan, as judged by the investigator.

24. Claustrophobia.

25. MRI-incompatible permanent cardiac pacemaker, automatic internal cardioverter.

26. Metallic implant (eg, defibrillator, neurostimulator, hearing aid, permanent use of infusion device, dental brace, metal-containing tattoo ink)[d].

27. Criterion modified per Amendment 3
27.1
    - Cardiac arrythmia assessed severe by the investigator
    - Conditions that could interfere with proper cardiac gating, eg, atrial fibrillation, multiple premature ventricular or atrial contractions.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. See Section 6.6 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements, monthly pregnancy testing in Section 5.1).

5.4. Screen Failures

For participants who failed screening, the following data will be recorded in the eCRF if available: reason for screening failure and baseline data collected until confirmation of the screening failure.

[d] Local MRI team's advice should be sought in case of doubt.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, if the reason for non-eligibility was transient (eg, abnormal laboratory test, insufficient wash-out period of an exclusionary medication). All screening assessments must have been made within 28 days before Day 1. Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit to reassess eligibility during the screening period. If a participant does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the participant eligibility criteria, the participant may be rescreened on one occasion only. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification.

6. STUDY INTERVENTION

6.1. Description of Study Intervention

Manufacturing, labeling, packaging, and supply of study intervention will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and any local or national regulatory requirements.

Selexipag will be manufactured and provided under the responsibility of the sponsor. See the Investigator's Brochure[16] for a list of excipients.

All study intervention supplies are to be used only in accordance with this protocol and not for any other purpose.

Study intervention is labeled to comply with the applicable laws and regulations of the countries/territories in which the study sites are located. Labels must remain affixed to the bottles.

Open-label selexipag will be provided as round, debossed, film-coated tablets in childproof bottles.

Study intervention name:	Selexipag
Dosage formulation	Round, film-coated tablets

Unit dose strengths/ Dosage levels:	200 µg: light-yellow, film-coated tablets with "2" debossed on one side 400 µg: red, film-coated tablets with "4" debossed on one side 600 µg: light-violet, film-coated tablets with "6" debossed on one side 800 µg: green, film-coated tablets with "8" debossed on one side 1000 µg: orange, film-coated tablets with "10" debossed on one side 1200 µg: dark-violet, film-coated tablets with "12" debossed on one side 1400 µg: dark-yellow, film-coated tablets with "14" debossed on one side 1600 µg: brown, film-coated tablets with "16" debossed on one side
Route of administration	Oral
Dosing instructions	One dose twice daily (in the morning and in the evening), with or without food.

6.2. Study Intervention Administration

The tablets will be administered orally and should be swallowed whole (ie, not crushed, split, or chewed) with water.

On Day 1, the participant will receive only 1 dose, and at each dose change, the first intake of the new dose is to be taken in the evening to reduce the likelihood of the occurrence of prostacyclin-associated AEs. Tolerability may improve when study intervention is taken with food. Participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s) will start with 200 µg qd in the morning of Day 2.

For a definition of study intervention overdose, see Section 6.9.

Study intervention administration must be captured in the source documents and the eCRF. Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

6.2.1. Study Intervention Up-Titration

Based on the GRIPHON study, the effect of selexipag on the composite endpoint of death from any cause or a complication related to PAH is consistent across different IMDs. The goal of the up-titration is to permit each participant to reach his/her personal highest tolerated dose without unmanageable prostacyclin-associated adverse effects.

Study intervention will be up-titrated to allow each participant to reach their IMD, in the range of 200 to 1,600 µg twice daily.

The study intervention will be up-titrated from Day 1 to the end of Week 12 (Day 84). Dosing will start at 200 µg twice daily. 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 (Table 2) if possible. Up-titration will be flexible and may be adapted in case of adverse effects that cannot be relieved with symptomatic treatment[e]. In this case, the site may either postpone up-titration by 1 week or down-titrate study intervention.

[e] Such as headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing.

The dose reached at the end of Week 12 will be considered the participant's IMD and will be maintained until EOT.

Table 2: Up-Titration Guide

Weeks	Days	Target selexipag dose (µg, twice per day)[a]	Comments
1	1-7	200	In case of adverse effects that cannot be relieved with symptomatic treatment, postponement of up-titration by 1 week or down-titration should be considered.
2	8-14	400	
3	15-21	600	
4	22-28	800	
5	29-35	1000	
6	36-42	1200	
7	43-49	1400	
8	50-56	1600	
9-12	57-84	Buffer period to permit up/down-titration to ensure IMD is reached at the end of Week 12.	
13-52	85-364	IMD	

IMD individual maintenance dose

[a] 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.

6.2.2. Study Intervention Maintenance

The maintenance phase will consist of treatment at the participant's IMD from the start at Week 13 to the end of Week 52.

6.3. Preparation/Handling/Storage/Accountability

Study intervention supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label. See the pharmacy manual/study-site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Participants will be asked to return all used, partially used, and unused study intervention bottles at each visit. The protocol-mandated study intervention dispensing procedures may not be altered without prior written approval from the sponsor. The interactive web response system will allow dispensation of study intervention outside scheduled visits. An accurate record of the date, strength, and amount of study intervention dispensed to each participant must be available for inspection at any time.

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention (strength

and number of dispensed bottles and date dispensed/strength and number of tablets dispensed) to the participant, and the return of study intervention (date returned/strength and number of tablets returned) from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers. If the participant forgets to bring the remaining study intervention to a study visit, participant must be instructed to not take any tablets from the remaining study intervention bottle and to return it at the next visit.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as, but not limited to, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants enrolled in the study. The participants will receive sufficient study intervention to cover the period up to the next scheduled visit. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions will be provided in the pharmacy manual/study-site investigational product and procedures manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

As this is an open-label study, randomization and blinding procedures are not applicable.

6.5. Study Intervention Compliance

Study intervention compliance will be based on study intervention accountability. Study intervention compliance will be calculated by site personnel at each site visit using the below formula and entered in the eCRF:

For each strength dispensed:

Compliance [(number of tablets dispensed number of tablets returned) / total number of tablets that should have been taken during the period[f]] × 100.

Between visits, compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as a protocol deviation, which will be reported in the clinical trial management system by the clinical research associate. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the study intervention. This discussion and its outcome must be documented in the source documents.

6.6. Concomitant Therapy

A participant may be enrolled only if therapies received before Day 1 comply with eligibility criteria.

From Day 1 to completion of EOT assessments, the following therapies are forbidden and will lead to study intervention discontinuation:

- Strong inhibitors of CYP2C8 (eg, gemfibrozil)
- Prostacyclin, prostacyclin analog, or any other agent acting on the prostacyclin pathway, except iv selexipag in the US for participants who are temporarily (maximum of 14 days; see Section 7.2) unable to take the study intervention orally
- Any other investigational drug

From Day 1 to completion of EOT assessments, the following therapies may be initiated or up-titrated (if applicable) if documented symptoms lead to the decision to escalate PAH treatment before Week 52 assessments:

- sGCs
- ERA
- PDE-5i
- Any other PAH-specific therapy that would become commercially available, provided it is not acting on the prostacyclin pathway

6.7. Study Intervention Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or sub-investigator), unless an immediate safety risk appears to be present. See Section 6.2.1 for titration of study intervention during the first 12 weeks of treatment.

For participants with moderate hepatic impairment (Child-Pugh Class B) or using moderate inhibitors of CYP2C8 (eg, clopidogrel, deferasirox, teriflunomide, leflunomide) concomitantly with the study intervention, dosing frequency of study intervention must be reduced to once a day. Dosing

[f] According to the study intervention administration log

frequency of selexipag should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped[16].

It has been shown that, when moderate or strong inducers of CYP2C8 are used in combination with selexipag, the exposure to selexipag active metabolite is reduced by half. Dose adjustment of selexipag may be required with concomitant administration of inducers of CYP2C8 (eg, rifampicin, carbamazepine, phenytoin).

The effect of strong inhibitors of UDP-glucuronosyltransferase (UGT)1A3 and UGT2B7 (eg, valproic acid, probenecid, and fluconazole) on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration may result in an increase in exposure to the active metabolite. Therefore, caution is required when these medicinal products are administered concomitantly with selexipag.

6.8. Continued Access to Study Intervention After the End of the Treatment Period

Local regulations on continued access will always take precedence.

At the end of their participation in the treatment period, participants who benefit from the study intervention as assessed by the treating physician will be offered the opportunity to continue receiving selexipag via the following options:

- Switch to commercial selexipag, applicable to participants who reside in a country/territory where selexipag is approved, commercially available and reimbursed for the treatment of participant's PAH.
- Switch to a PTA program which will be set up for participants who reside in countries/territories where selexipag is not yet commercially available or not reimbursed for the participant's PAH, if allowed as per local regulations.
- Switch to another open-label clinical study with selexipag, applicable for participants who reside in a country/territory where the conduct of such study is approved by the local health authorities and where the 2 options above are not applicable.

6.9. Overdose

Overdose is defined by the intake of a dose >1,600 µg or a total daily dose >3,200 µg. For participants with moderate hepatic impairment or who are concomitantly taking moderate CYP2C8 inhibitor(s), the dosing frequency is once daily and overdose is defined by the intake of a dose >1,600 µg or a total daily dose >1,600 µg.[16]

Isolated cases of overdose up to 3,200 µg were reported. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required.

In the event of a selexipag overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.

- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until selexipag can no longer be detected systemically (at least 3 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
- Institute supportive therapy as clinically indicated. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein bound.

For more information see Section 10.4.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

The decision to prematurely discontinue study intervention may be made by the participant, the investigator, or sponsor personnel. A participant has the right to prematurely discontinue study intervention at any time, without any justification, by withdrawal from study intervention only or by withdrawal from any further participation in the study. The investigator must discontinue study intervention for a given participant if, on balance, investigator believes that continued administration would be contrary to the best interests of the participant.

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety or tolerability reasons, it is in the best interest of the participant to discontinue study intervention.
- The female participant becomes pregnant (see Section 10.5).
- The participant develops severe hepatic impairment. If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If a participant has developed severe hepatic impairment (Child-Pugh Class C) at any time during the study, the study intervention must be permanently discontinued (see Section 10.8).
- The participant develops pulmonary edema due to PVOD. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered. If confirmed, the study intervention must be discontinued.
- Planned initiation of prohibited treatments during the treatment period.
- Study intervention interruptions exceeding 14 consecutive days.

If a participant discontinues study intervention for any reason (except withdrawal of consent from any further participation in the study) before scheduled EOT at Week 52, participant will continue to attend the visits and assessments as scheduled (ie, premature EOT and EOS visits), provided the participant's consent for this limited participation in the study has not been withdrawn. If the

reason for withdrawal from the study is withdrawal of consent from any further participation in the study, then no additional assessments will be permitted.

7.2. Temporary Interruption of Study Intervention

Study intervention may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons.

Interruptions of study intervention must be kept as short as possible. In case of study intervention interruption between 3 to 14 days, study intervention should be re-started at a lower dose at the discretion of the investigator, and then titrated to the pre-interruption dose. For each participant, the up-titration frequency will be up to the medical judgment of the investigator and based on his/her clinical evaluation of the participant's tolerability of the study intervention prior to its interruption (see Section 6.2.1). Re-uptitration can be done at scheduled or unscheduled telephone calls or visits.

Study intervention interruptions exceeding 14 consecutive days must lead to permanent discontinuation of study intervention (see Section 7.1).

Interruptions of 1 day or more must be recorded on the study intervention log in the eCRF.

7.3. Participant Discontinuation/Withdrawal from the Study

A participant will not be automatically withdrawn from the study if participant has to discontinue study intervention before the end of the intervention regimen (Section 7.1).

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up (Section 7.4)
- Withdrawal of consent from any further participation in the study
- Death
- Participant is poorly compliant with study procedures, visits, and assessments, preferably after evaluation and discussion between the investigator and the sponsor
- The investigator believes that continued participation in the study would be contrary to the best interests of the participant
- Sponsor's decision for any reason, including but not limited to premature termination or suspension of the study

If a participant discontinues study intervention and withdraws from the study before the EOS visit for any reason (except for death, loss to follow-up, or withdrawal of consent from any further participation in the study), every attempt should be made to schedule a last appointment/telephone call to assess the safety and well-being of the participant, collect unused study intervention, and discuss follow-up medical care. The investigator must provide follow-up medical care for all participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 6.7.

When a participant withdraws before study completion, the reason for withdrawal (if known) is to be documented in the eCRF and in the source document.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. Withdrawal of consent should be an infrequent occurrence in clinical studies,[23] therefore, prior to the start of the study, the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

Circumstances for Reduced Follow-up

Only in a situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up. These may include (as local regulations permit):

- Less frequent clinical visits
- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

7.4. Lost to Follow-up

Prior to enrollment, measures should be taken to reduce the chances of a participant being deemed lost to follow-up. These measures include attempts to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the

participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, participant will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach participants to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The schedule of activities (Table 1) summarizes the frequency and timing of efficacy, safety, and exploratory assessments applicable to this study.

For all visits, the participants must be seen or called on the designated day with an allowed visit window indicated in the schedule of activities. Efficacy assessments at EOT must be performed at trough (ie, morning dose NOT taken). A follow-up safety telephone call/visit must be performed at least 30 days after intake of the last dose of study intervention. If it is not possible to complete all assessments on the same day, a visit may extend over more than 1 day within the allowed time window.

All study assessments will be performed by qualified study personnel (medical, nursing, or specialist technical personnel) and will be recorded in the eCRF, unless otherwise specified. Actual dates of assessments will be recorded in the eCRF.

The total blood volume to be collected from each participant will be approximately 69 mL (Table 3).

Table 3: Volume of Blood to be Collected From Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
Hematology	2	3	6
Clinical chemistry	6	3	18
Serum β-hCG pregnancy tests[b]	2.5	3	7.5
NT-proBNP sample	2.5	3	7.5
Biomarker samples	10	3	30
Approximate total[c]	**23**		**69**

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] For women of childbearing potential.
[c] Repeated or unscheduled samples may be taken for safety reasons or technical issues with the samples.
hCG human chorionic gonadotropin; NT proBNP N terminal pro hormone brain natriuretic peptide.

Unscheduled Visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit, appropriate assessments may be performed based on the judgment of the investigator.

After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

See the schedule of activities (Table 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples will be provided in the laboratory manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure.
- Pharmacy manual/study site investigational product and procedures manual.
- MRI image acquisition protocol (IAP) and Echo IAP.
- Sponsor guidance for 6MWT.
- Laboratory manual, requisition forms, and sampling supplies.
- Participant experience questionnaire EQ-5D-3L in local language(s).
- Interactive web response system manual (IWRS).

- eCRF completion guidelines.
- SAE form and completion guideline.
- Pregnancy notification forms.
- Product Quality Complaint (PQC) forms.
- Study participant cards.
- Sample ICFs.

8.1. Demographics and Baseline Characteristics

Demographic and baseline PAH characteristic data to be collected on all enrolled participants include: age, sex, race and ethnicity (where local regulations permit), weight and height, date of the initial PAH diagnosis by RHC and WHO FC at screening.

8.2. Medical History

All relevant medical history/current medical conditions based on the investigator's judgment (eg, chronic and ongoing acute conditions, serious past conditions) or for which the participant receives a treatment and that are ongoing before and/or at the time of signing informed consent will be recorded on the medical history page. Where possible, diagnoses and not symptoms will be recorded.

8.3. Efficacy Assessments

8.3.1. Imaging

8.3.1.1. Expert Reviewers

A team of independent expert MRI reviewers and a team of independent expert Echo reviewers will be selected, based on their qualifications and experience. For their respective imaging modality (MRI or Echo), they will be responsible for:

- Reviewing and approving the IAP
- Writing the variable assessment charter
- Quality control of images
- Central assessment of imaging according to the charter.

IAPs and variable assessment charters will be reviewed by the sponsor.

8.3.1.2. Site Qualification

Participating sites will need to be qualified for MRI and Echo before enrolling participants. Qualification will be performed in 2 steps: first, a questionnaire describing the site's MRI/Echo equipment will be reviewed by one of the appropriate expert reviewers. Second, if the questionnaire is approved, the site will submit imaging of a volunteer, performed according to the

IAP. Sites will be qualified if an expert reviewer confirms that imaging quality is appropriate for the study.

Sites who previously demonstrated suitable imaging quality in any other of the sponsor's studies will be qualified for MRI/Echo by confirming that the equipment and imaging team for this study are those that previously proved appropriate.

8.3.1.3. Image Acquisition

Imaging will be performed as described in the MRI IAP/Echo IAP.

8.3.1.4. Quality Control

For each enrolled participant, expert reviewers will control the quality of imaging as it becomes available.

8.3.1.5. Imaging Assessment

After an individual participant's Week 26 or Week 52 imaging assessments, a single reviewer will read all scans (MRI or Echo) of that participant at once. For this review, expert reviewers will be blinded to the participant and timepoint and will assess variables according to the MRI/Echo review charter.

8.3.2. 6MWT

Exercise capacity will be measured by the 6MWT. The 6MWT is a non-encouraged test that measures the distance walked in 6 minutes. It will be performed according to sponsor guidance (Section 10.9).

At Week 26 and EOT visit, participants must NOT take the morning study intervention dose before any visit-related procedure.

Dyspnea will be assessed by the Borg CR 10 Scale®, a scale used to quantify the degree of shortness of breath before and at the end of the 6MWT (Section 10.9).

8.3.3. WHO FC

WHO FC will be determined as per WHO definition (Section 10.6).

8.3.4. Risk Stratification

Clinical signs of right heart failure, progression of PAH symptoms, and syncope will be collected at screening and Week 26 visit; and will be used for risk stratification.

8.3.5. NT-proBNP

A blood sample will be drawn for the analysis of NT-proBNP. NT-proBNP results will be assessed by the central laboratory. Details regarding blood sampling procedures, collection, and shipment of the samples will be described in the laboratory manual.

8.3.6. Biomarkers

It is hypothesized that selexipag may have a beneficial effect on circulating biomarkers involved in RV function and structure; therefore, changes in such biomarkers from baseline to Week 26 and Week 52 will be explored.

Serum samples will be stored. They will be used to assess additional exploratory biomarkers after the EOS at study level. These additional exploratory biomarkers will be based on the latest scientific evidence regarding RV function and structure at the time of laboratory analysis (Section 10.2). No genetic testing of any kind will be performed.

The exploratory biomarkers may be analyzed by different laboratories; each analyte will be analyzed by the same laboratory for all participants.

8.4. Safety Assessments

The standard assessments to evaluate the safety and tolerability of selexipag in this study include reporting and follow-up of (S)AEs, pregnancies, physical examination, vital signs, and safety laboratory tests from signing of ICF onwards until the EOS visit (see Section 4.4) (Table 1).

AEs will be reported and followed by the investigator as specified in Section 8.5 and Section 10.4.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the EOS/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached or until the participant has been deemed lost to follow-up (see Section 7.4).

8.4.1. Physical Examination

Physical examination will include the evaluation of the participant's height (only at screening), the general appearance, heart and lungs. Other examinations will be performed if indicated, based on medical history and/or symptoms.

Height will be measured without shoes.

Physical examination findings made after signing of informed consent, which meet the definition of an AE must be recorded on the Adverse Event page of the eCRF.

8.4.2. Vital Signs

Heart rate (HR), SBP, diastolic blood pressure (DBP) and body weight, will be assessed during on-site visits.

Blood pressure and pulse/heart rate measurements will be assessed in a supine or sitting position with an automated device. Manual techniques will be used only if an automated device is not available. It is recommended that the participant is allowed to rest for at least 5 minutes before the measurement. It is also recommended that measurements are performed on the same arm and in

the same position (supine or sitting) throughout the study for each individual participant. Vital signs are to be measured prior to blood collection.

Body weight will be measured in indoor clothing without shoes.

8.4.3. Clinical Safety Laboratory Assessments

Blood samples for clinical chemistry and hematology will be collected as noted in Section 10.2.

Safety laboratory results will be assessed by the central laboratory. Safety laboratory analyses will include:

- Basic hematology panel
- Clinical chemistry panel including thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4)
- Pregnancy tests for females of childbearing potential. A serum pregnancy test will be performed at the site at screening, at Week 26 and at Week 52 (EOT); urine pregnancy tests will be performed at the site on Day 1, and at the participant's home monthly between Day 1 and EOS, except for Month 6 and Month 12, when a serum pregnancy test is performed at the site visit (Weeks 26 and 52). The site will call female participants of childbearing potential monthly to check the pregnancy test result.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate and filed with the source documents. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of informed consent must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities detected after signing of informed consent must be reported as an AE or SAE as appropriate (see Section 8.5 and Section 10.4).

8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.4.

8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations (Section 10.4), whether serious or non-serious, will be reported on specific Adverse Event pages of the eCRF throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4) or date of last contact (see Section 7.3).

Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator until EOS, must be reported on Adverse Event pages in the eCRF and on the Serious Adverse Event form, whether or not this event is considered by the investigator to be related to study intervention.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax) or email. Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.5.2. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.5.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs).

The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.5.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate Pregnancy Notification Form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the newborn will be required. The duration of this follow-up will depend on the clinical conditions of the newborn and may be extended until discharge from hospital when applicable.

Any SAE occurring during the pregnancy must be reported as described in Section 10.4.

8.6. Participants' Experience

Participants' experience will be assessed with the 3-level version of EQ-5D (EQ-5D-3L) questionnaire during Day 1, and at Week 26 and Week 52 (EOT) at the site.

The EQ-5D-3L questionnaire has 2 components: health state description and visual analogue scale (EQ VAS) for participant's self-rating. In the description part, health status is measured in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression at 3 levels: no problems, some problems, and extreme problems. See Section 10.7.

If an event meeting the definition of an AE is reported by a participant in the context of a questionnaire, it is the physician's responsibility to report it as an AE in the eCRF form.

8.7. Genetics

Genetics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

The null statistical hypothesis is that the mean change from baseline to Week 26 in RVSV is equal to zero. The alternative statistical hypothesis is that the mean change from baseline in RVSV is different from zero.

9.2. Sample Size Determination

Sample size calculation for the primary endpoint is 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-evaluable 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.[35] The associated SD of 20 mL is justified by the REPAIR study interim analysis on 42 participants, where the observed mean change (SD) from baseline to Week 26 was +16.6 mL (16.34).

Table 4 displays power calculations for different assumptions of treatment effect and associated SD, given a fixed number of 68 analyzable participants (80 in total).

Table 4: Sample Size Power Sensitivity

Scenario	Change from baseline to Week 26 in RVSV (mL)	Associated SD	Power
Retained scenario	8	20	90%
Sensitivity 1	8	22	84%
Sensitivity 2	8	25	74%
Sensitivity 3	10	20	98%
Sensitivity 4	10	22	96%
Sensitivity 5	10	25	90%

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

- **Screened Analysis Set:** The Screened Analysis Set will include all participants who were screened and received a participant number.
- **Safety Set:** The Safety Set (SS) will include all participants from the Screened Analysis Set who received at least 1 dose of study intervention.
- **Full Analysis Set:** The Full Analysis Set (FAS) will include all participants from the SS who had a baseline as well as a postbaseline measurement for RVSV assessed by cardiac MRI from pulmonary artery flow.
- **Per-protocol Analysis Set:** The Per-Protocol Analysis Set (PPS) will include all participants in the FAS without major protocol deviations that could affect the main analysis of the primary efficacy variable.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1. General Considerations

The overall type I error is α 0.05. All analyses will be performed using 2-sided statistical tests.

If the primary endpoint analysis is statistically significant (ie, p-value below nominal alpha), the study will be declared positive.

No multiplicity adjustments will be performed for secondary/exploratory endpoints, and therefore, all associated p-values are of exploratory nature. No interim analysis will be performed.

Participants without a baseline value will be excluded from the corresponding analysis.

Subgroup analyses on primary and secondary endpoints will include WHO FC (II/III) at baseline. Additional subgroup analyses will be specified in the SAP. All subgroup analyses will be of exploratory nature.

9.4.2. Primary Endpoint

The primary efficacy analysis will be performed on the FAS. RVSV will be summarized by timepoint (baseline and Week 26) using descriptive statistics (n, mean, SD, median, Q1 and Q3). The change from baseline to Week 26 in RVSV will be summarized similarly.

Change from baseline in RVSV will be analyzed at α 0.05 (2-sided) using an analysis of covariance (ANCOVA) with a factor for WHO FC (II/III) at baseline and a covariate for baseline RVSV. The mean change from baseline and 95% CI will be estimated based on the model.

A sensitivity analysis will be performed on the PPS. Another sensitivity analysis will be performed on the SS, where participants with missing postbaseline RVSV will be imputed using their baseline value.

9.4.3. Secondary Endpoints

Change from baseline to Week 26 in RVEDV, RVESV, RVEF, RV mass, RVGLS, 6MWD, and number of low-risk criteria will be summarized descriptively by timepoint and analyzed at α 0.05 (2-sided) on the FAS using an ANCOVA with a factor for WHO FC (II/III) at baseline and a covariate for baseline value. The mean change from baseline and 95% CI will be estimated based on the model.

WHO FC will be summarized on the FAS by timepoint using frequency tables. Changes from baseline in WHO FC will be dichotomized as worsening (ie, change >0) versus no change or improvement (ie, change ≤0). Worsening will be analyzed at α 0.05 (2-sided) using a logistic regression model with a factor for WHO FC (II/III) at baseline.

NT-proBNP will be summarized on the FAS by timepoint using descriptive statistics as well as geometric means and CVs. The Week 26 versus baseline ratio will be summarized similarly. The ratio versus baseline in NT-proBNP will be log-transformed and analyzed at α 0.05 (2-sided) using an ANCOVA with a factor for WHO FC (II/III) at baseline and a covariate for baseline log NT-proBNP.

As described in Section 9.4.1, all analyses for secondary endpoints are of exploratory nature because there will be no adjustment for multiplicity. Additional analyses will be performed on the SS for all secondary endpoints, where participants with missing postbaseline value will be imputed using their baseline value.

9.4.4. Exploratory Endpoints

Exploratory variables will be analyzed at α 0.05 (2-sided) on the FAS and SS. Details will be specified in the SAP.

Biomarker exploratory analyses (Section 8.3.6) will be specified in a separate specific SAP.

9.4.5. Safety Analyses

Safety analyses will be performed on the SS.

Adverse Events

A treatment-emergent AE is any AE from first dose up to 3 days after end of study intervention. The number and percentage of participants experiencing at least 1 treatment-emergent AE or SAE will be tabulated by:

- Medical Dictionary for Regulatory Activities system organ class and individual preferred term, in descending order of incidence.
- Frequency of participants with events coded with the same preferred term, in descending order of incidence.

Furthermore, treatment-emergent AEs and SAEs will be tabulated as described above by severity and relationship to study intervention. SAEs will be also tabulated up to 30 days after end of study intervention.

AEs leading to premature discontinuation of study intervention, AEs with an outcome of death, and AEs of special interest will be summarized as described above. The detailed list of AEs of special interest will be specified in the SAP.

AEs occurring during titration period will also be summarized separately.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings, as well as narratives, will be provided for SAEs, for AEs leading to premature discontinuation of study intervention, and for AEs with an outcome of death.

The following AEs will be listed only:

- AEs occurring prior to first study intervention dose
- Non-serious AEs occurring after EOT + 3 days
- SAEs occurring more than 30 days after discontinuation of study intervention

Clinical Laboratory Tests

Descriptive summary statistics by visit will be provided for observed values and absolute changes from baseline, in both hematology and clinical chemistry laboratory tests. In order to minimize missing data and to allow for out-of-window visits, all recorded assessments up to EOT + 3 days will be assigned to the most appropriate visit timepoint according to the best fitting time window for that assessment.

The sponsor's internal guidelines will be used for the definitions of marked abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables will be transformed to standard units. All laboratory data transferred will be taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

Marked laboratory abnormalities will be summarized for each laboratory variable providing their incidence and frequency. Absolute values and changes from baseline of laboratory values during the course of the study will also be summarized.

The number and percentage of participants with treatment-emergent laboratory abnormalities will be tabulated.

Physical Examinations

Physical examination findings will be listed.

9.5. Interim Analysis

Not applicable.

9.6. Data Monitoring Committee

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

6MWD	6-minute walking distance
6MWT	6-minute walking test
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
CBC	Complete blood count
CHF	Congestive heart failure
CI	Confidence interval
CV	Coefficient of variation
4D	4-dimensional
Echo	Echocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
EQ-5D	EuroQol 5-Dimension scale
ERA	Endothelin receptor antagonist
FAS	Full Analysis Set
FC	Functional class
HIV	Human immunodeficiency virus
IAP	Image Acquisition Protocol
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements
IEC	Independent Ethics Committee
IMD	Individual maintenance dose
INR	International normalized ratio
IP	Prostacyclin
IRB	Institutional Review Board
iv	Intravenous
LV	Left ventricle, left ventricular
LVEDV	Left ventricular end-diastolic volume

LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVSV	Left ventricular stroke volume
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
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
PDE-5i	Phosphodiesterase type 5 inhibitor
PPS	Per-Protocol Set
PT	Prothrombin time
PTA	Post-trial access
PVR	Pulmonary vascular resistance
RA	Right atrium, right atrial
RBC	Red blood cell
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
sGCs	Soluble guanylate cyclase stimulator
SS	Safety Set
SUSAR	Suspected unexpected serious adverse reaction
T3	Tri-iodothyronine

T4	Thyroxine
TSH	Thyroid-stimulating hormone
UGT	UDP-glucuronosyltransferase
WBC	White blood cell
WHO	World Health Organization
WU	Wood unit

10.2. Appendix 2: Clinical Laboratory Tests

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

The following tests will be performed according to the Schedule of Activities by a central laboratory:

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count RBC count Hemoglobin Hematocrit MCV RBC morphology	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.	
Clinical Chemistry	Sodium Potassium Creatinine Glomerular filtration rate, using the Modification of Diet in Renal Disease formula AST ALT Total and direct bilirubin Alkaline phosphatase Thyroid hormones: Free and total triiodothyronine (T3) Free and total thyroxine (T4) Thyroid stimulating hormone (TSH)	
NT-proBNP	NT-proBNP	
Pregnancy	Serum pregnancy testing for women of childbearing potential only	
Biomarkers	Biomarkers: Exploratory biomarkers to be measured after the end of the study at study level will be based on the latest scientific evidence regarding RV function and	

Laboratory Assessments	Parameters
	structure at the time of laboratory analysis. No genetic testing of any kind will be performed.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and

agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country/Territory Selection

This study will only be conducted in those countries/territories where selexipag is available or where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent

should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by Health Authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

A participant who is rescreened is not required to sign another ICF.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

10.3.4. DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection.

This informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand selexipag, to understand PAH, to understand differential intervention responders, and to develop tests/assays related to selexipag and PAH. The research may begin at any time during the study or during the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research.

10.3.6. COMMITTEES STRUCTURE

Steering Committee

A steering committee is involved in the study design and will provide guidance on the study conduct and study publications. The committee is governed by a dedicated Steering Committee charter.

MRI Expert Reviewers

A committee of expert MRI reviewers will review and approve the MRI IAP, write the variable assessment charter, perform quality control of images, and assess imaging variables according to the charter.

Echo Expert Reviewers

A committee of expert Echo reviewers will review and approve the Echo IAP, write the variable assessment charter, perform quality control of images, and assess imaging variables according to the charter.

10.3.7. PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding selexipag or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of selexipag, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

All participative measurements (eg, questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (EDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Date of an RHC performed before initiation of selexipag and associated mPAP, CO, HR, and either PAWP or LVEDP.
- Date of a pulmonary function test performed before initiation of selexipag and associated diffusing capacity of the lung for carbon monoxide (or CT scan summary), forced vital capacity (% predicted), and forced expiratory volume in 1 second (% predicted).
- Documentation confirming absence of hepatic impairment. If known or documented hepatic impairment, all components used for the assessment of Child-Pugh Class should be documented.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be used, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is used, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. MONITORING

The sponsor will use a combination of monitoring techniques: central, remote, and on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

Study Safety Monitoring

Study safety information (AEs, SAEs, laboratory values, physical examinations, as required) will be monitored and reviewed on a continuous basis by the sponsor's clinical trial team. The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (eg, medical imaging, local laboratory values) for the purpose of safety monitoring. Such additional data may be shared with external experts.

10.3.12. ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first informed consent signed is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local Health Authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.4.1. ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.5.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event, the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For selexipag, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.[16]

10.4.2. ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention (see Section 6.9).
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention

- Any failure of expected pharmacologic action (ie, lack of effect if used according to the local label) of a sponsor study intervention (to be reported as a PQC for marketed products)
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a sponsor medicinal product (with or without participant exposure to the sponsor medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding
- Reporting of participant pregnancy or participant partner pregnancy

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF and reported on SAE Form.

10.4.5. PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

Serious Adverse Events

- Refer to Section 8.5 for more information on the reporting procedures of SAEs. All SAEs that have not resolved at time of the EOS visit (see Section 4.4) must be followed until any of the following occurs: The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up [see Section 7.4])

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility, cosmetic elective surgery).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF) or standard monitoring of a pre-existing disease or medical condition that did not worsen, eg, hospitalization for coronary angiography in a participant with stable angina pectoris. Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

If the participant is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted by facsimile (fax).

10.4.6. PRODUCT QUALITY COMPLAINT HANDLING

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.5.1). A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. CONTACTING SPONSOR REGARDING SAFETY, INCLUDING PRODUCT QUALITY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.5.4, Pregnancy and Section 10.4 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**

  Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

  Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin an acceptable method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation oral injectable
• Male or female condom with or without spermicide[b]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[b]
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

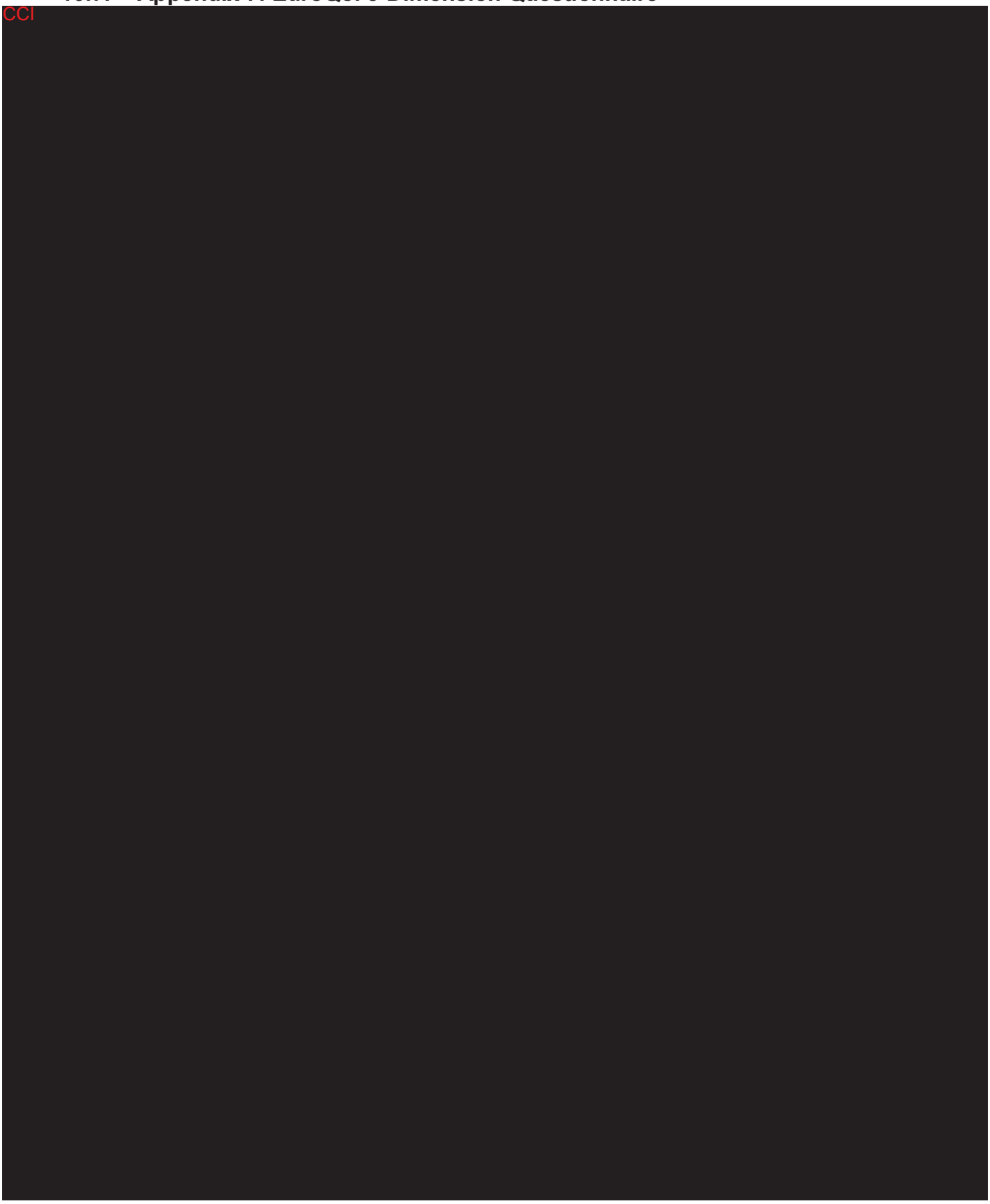
If a female participant becomes pregnant while on study intervention, study intervention must be discontinued and the investigator should arrange for specific therapy as needed.[21] For reporting of pregnancies, refer to Section 8.5.4.

10.6. Appendix 6: WHO Functional Classification of Pulmonary Hypertension

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

10.7. Appendix 7: EuroQol 5-Dimension Questionnaire

CCI



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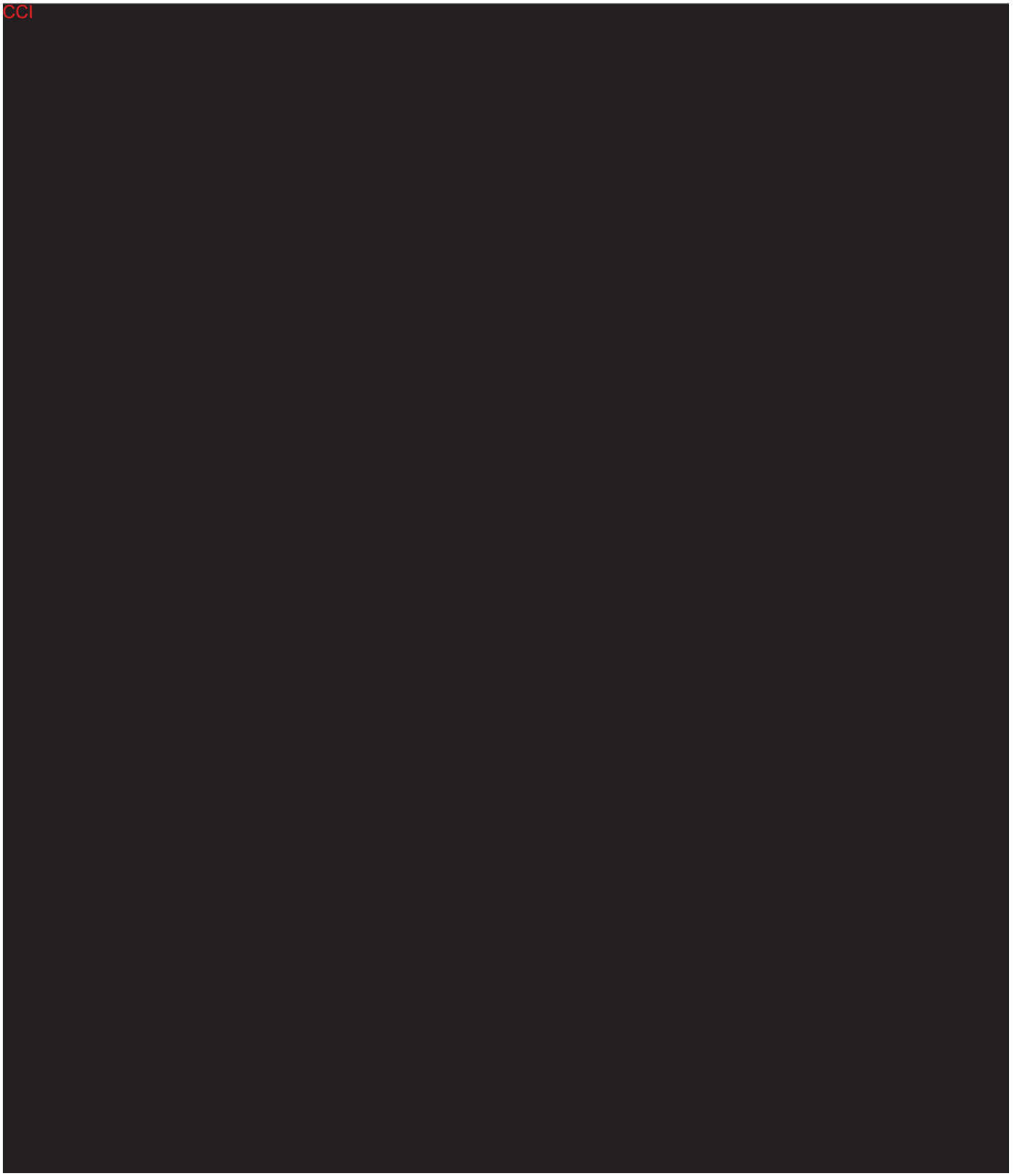


10.8. Appendix 8: Child-Pugh Classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to the Table 5.[7,8]

Table 5: Child-Pugh classification

	Score		
	1	**2**	**3**
Total bilirubin (mg/dL)	<2.0	2.0 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 3.5	<2.8
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy*	Grade 0	Grade 1 2	Grade 3 4
Prothrombin time (seconds prolonged)	<4	4 6	>6
or			
INR	<1.7	1.7 2.2	>2.2

*Hepatic encephalopathy scoring will be based on the following criteria:
• Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram.
• Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves.
• Grade 2: lethargic, time disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
• Grade 3: somnolent, stuporous, place disoriented, hyperactive reflexes, rigidity, slower waves.
• Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 3 cycles per second delta activity.

- Class A: Score 5-6
- Class B: Score 7-9
- Class C: Score 10-15

10.9. Appendix 9: Sponsor 6-Minute Walk Test Guidance

This document stipulates the criteria under which study-required 6MWTs will be carried out in Clinical Protocol 67896049PAH4005 (Amendment 3).

These criteria are, in part, derived from the recommendations included in the ATS Guidelines issued in 2002 and the ERS/ATS Technical Standard published in 2014.[2,14] As opposed to the comprehensive published manuscripts, this guidance has been shortened and accustomed for use in a clinical study in which a variety of different assessments may need to be performed at a given visit. In addition, dyspnea will be assessed using the Borg CR 10 Scale®.[5]

10.9.1. INSTRUCTIONS

General

The 6-Minute Walk Test (6MWT) must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track length for the 6MWT must be free of obstacles. The use of treadmill and a continuous course, eg, a circuit, is not allowed.

The ideal track length used for the 6MWT is 30 meters (If the track is shorter, it must be no shorter than 20 meters in length). The track must be marked at regular intervals to facilitate measurement of the distance walked (markings every 3 meters are recommended). The turnaround points must be marked with a cone. A starting line, which marks the beginning and the end of each lap (one lap is twice the length of the track used at the site), needs to be marked on the floor.

Local safety practice regarding medical emergencies and contraindications for 6MWT must be followed at each participating site.

The person administering the 6MWT (tester) needs to stand near the starting line during the 6MWT, must not walk with the participant, and must not get distracted during the conduct of this 6MWT (eg, by talking to someone).

Rest periods are allowed if the participant can no longer continue. If the participant needs to rest, participant may pause, lean against the wall and continue walking whenever participant feels able. The timer must continue to run even if the participant stops to rest. The 6MWT can be stopped at any moment due to medical emergencies or safety issues such as chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

The 6MWT is a non-encouraged test. An even tone of voice must be used when using the standard phrases. No other instructions or words of encouragement are given during the test, other than the pre-scripted phrases. Eye contact and body language signaling the participant to speed up must be avoided during the test.

Whenever possible, for an individual participant, repeat 6MWTs must be conducted in the same corridor and by the same tester, and preferably at about the same time of the day (ie, within ± 2 hours of the baseline test) to minimize variability.

If a participant is oxygen dependent, the flow rate must remain constant from 30 minutes prior to each 6MWT until the completion of all protocol-mandated assessments after the 6MWT.

Additionally, the way oxygen is delivered (delivery device, application route, way of carrying delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.

Training Tests

For participants who have not previously performed a 6MWT, a training 6MWT must be performed before the first protocol-mandated 6MWT is performed.

Data from the training 6MWT are not collected in the CRF but must be documented in the source data.

Timing

Only two 6MWTs can be performed on the same day. The interval between two 6MWTs on the same day must be at least 2 hours.

10.9.2. TEST REQUIREMENTS

Participant

- The participant must wear comfortable clothing and appropriate walking shoes.
- The participant must not have exercised vigorously within 2 hours of beginning the test.
- It is recommended that the participant rests for at least 15 minutes before the test starts.
- It is recommended that participants receive their concomitant therapy on the day of the test. Study intervention must be taken after all study assessments have been performed. If the participant is used to take bronchodilators, participant must take them at least 10 to 30 min before the test.
- Participants can use their usual walking aids during the test (eg, cane). The same walking aid should be used for all 6MWTs. Walkers are not allowed.

Equipment to Perform the Test

- Countdown timer
- Mechanical lap counter
- Two cones to mark the turnaround points
- A chair that can be easily moved along the track
- 6MWT Worksheet
- Borg category-ratio (Borg CR 10 Scale®)

10.9.3. PERFORMING THE 6MWT

Assessments before the 6MWT

Before the 6MWT, the tester shows the Borg CR 10 Scale® to the participant and asks the participant:

- *"Please grade your dyspnea using this scale".*

The tester will record the baseline-6MWT dyspnea on the 6MWT the 6MWT worksheet.

Instructions to the Participant During the 6MWT

The tester uses the following exact dialogue with the participant:

> *"The objective of this test is to walk as far as possible in 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.*
>
> *You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."*

(The tester demonstrates the walking and pivots around a cone briskly).

> *"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember the object is to walk AS FAR AS POSSIBLE in 6 minutes, but don't run or jog."*

After these instructions are given to the participant, the tester says:

> *"Start now, or whenever you are ready."*

As soon as the participant starts to walk, the tester starts the timer and writes down start time. The tester reminds the participant of the elapsed time by saying:

> After the first minute: *"You are doing well. You have 5 minutes to go".*
>
> When the timer shows 4 minutes remaining: *"Keep up the good work. You have 4 minutes to go."*
>
> When the timer shows 3 minutes remaining: *"You are doing well. You are halfway done."*
>
> When the timer shows 2 minutes remaining: *"Keep up the good work. You have 2 minutes to go."*
>
> When the timer shows only 1 minute remaining: *"You are doing well. You have only 1 minute to go."*

If the participant stops walking during the test and needs a rest, the tester says:

> *"You can lean against the wall if you would like; then continue walking whenever you feel able."*

The tester will not stop the timer. If the participant stops before the 6 minutes are up and refuses to continue (or the tester decides that they should not continue), the tester wheels the chair over for the participant to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, the tester says:

> *"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."*

When the timer alarm rings the tester says:

> *"Stop!"*

Assessments After the 6MWT

The tester walks over to the participant, marks the spot where the participant stopped, records the total distance walked in the 6MWT worksheet and congratulates the participant on good effort.

After the 6MWT, the tester reminds the participant of their dyspnea and level of exertion that they chose before the 6MWT. The tester shows the Borg CR 10 Scale® to the participant and asks the participant:

- *"Please grade your dyspnea using this scale".*

The tester will record the post-6MWT dyspnea on the 6MWT worksheet.

10.9.4. 6MWT WORKSHEET

It is mandatory to use the 6MWT worksheet to capture documentation of each 6MWT newly performed for the purpose of the study and report relevant data in the eCRF, as indicated.

It is not mandatory to use the study 6MWT worksheet for historical 6MWTs.

10.9.5. HOW TO USE THE BORG CR 10 SCALE®

Instructions

The Borg CR 10 Scale® will be explained in detail to the participants at Screening before starting the first 6MWT (questionnaires and instructions will be provided in local language).

The tester will provide the following instruction to the participant:

"Use this rating scale to report how strong your perception of dyspnea is. First look at the verbal expressions. Start with them and then the numbers. Of these, ten (10) or "Extremely strong", "Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". If your feeling is "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", - "Extremely strong", "Maximal" you can use a larger number, eg, 12 or still higher (that's why "Absolute maximum" is marked with a dot "•").

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating dyspnea give a number that corresponds to how hard and strenuous you perceive your breathing to be. The perception of dyspnea is mainly the feeling that one cannot breathe well enough.

0 - "Nothing at all", means that you don't feel any shortness of breath.

1 - "Very weak" means a very light shortness of breath.

3 - "Moderate" is somewhat but not especially hard. You are somewhat shorter of breath.

5 - "Strong". Breathing is getting difficult. The effort to breathe is about half as intense as "Maximal".

7 - "Very strong" is quite strenuous. You can still breathe, but breathing is getting very difficult.

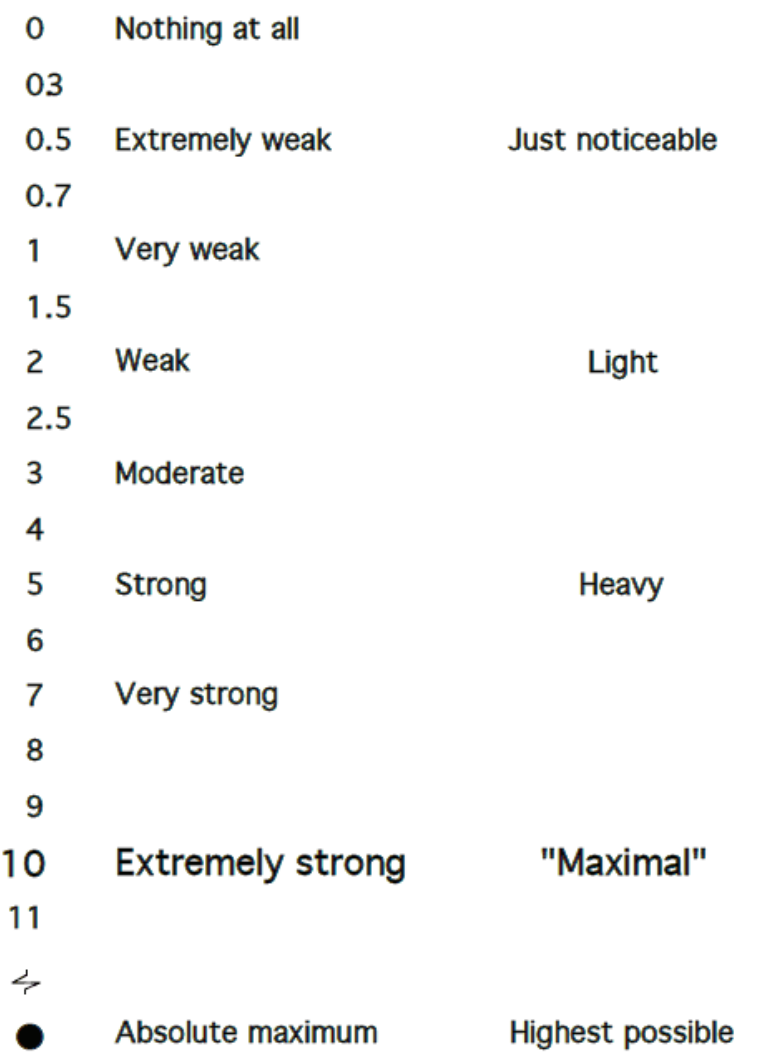
10 - "Extremely strong Maximal" is the greatest shortness of breath you have ever experienced in your life.

"•" - Is "Absolute maximum" for example "12" or even more.

Any questions?"

Borg CR 10 Scale®

The Borg CR 10 Scale® may be administered to the participant in an electronic format, ie, on a device such as a tablet, or in plain paper. If used in paper format, it must be printed on heavy paper (either DIN A4 or ANSI letter size and perhaps laminated) in 20-point type size.


0 Nothing at all
03
0.5 Extremely weak Just noticeable
0.7
1 Very weak
1.5
2 Weak Light
2.5
3 Moderate
4
5 Strong Heavy
6
7 Very strong
8
9
10 Extremely strong "Maximal"
11
Absolute maximum Highest possible
Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

6-MINUTE WALK TEST WORKSHEET

Clinical Protocol	Visit #	Participant Number #
67896049PAH4005 (Amendment 3)		

Was the 6MWT performed? ☐ Yes ☐ No
(if no, a qualified physician needs to provide a reason below for not performing the 6MWT)

If No, reason for not performing the 6MWT: ☐ Clinical Worsening ☐ Other

If Other: ☐ PH related ☐ Non-PH related

Administrative details	
Location of the corridor	---------- ----------
Corridor meets requirements as per Actelion 6-Minute Walk Test Guidance	☐ Yes ☐ No
Name of the tester performing the test	
Date of the 6MWT *(to be entered into the eCRF)*	⌊⌊⌋⌊⌊⌋⌊⌊⌋⌊⌊⌋⌊⌊⌋ dd MMM yy
Start time of the 6MWT (in 24-hour format) *(to be entered into the eCRF)*	⌊⌊⌋:⌊⌊⌋ HH : mm

Test preparation			
The participant wears appropriate clothing *(if no, this fulfills major protocol deviation criterion, please discuss with your site manager)*	☐ Yes	☐ No	
The participant wears appropriate walking shoes *(if no, this fulfills major protocol deviation criterion, please discuss with your site manager)*	☐ Yes	☐ No	
The participant exercised vigorously within 2 hours before the test *(if yes, this fulfills major protocol deviation criterion, please discuss with your site manager)*	☐ Yes	☐ No	
The participant has rested at least 15 minutes before the test	☐ Yes	☐ No	
The participant is used to taking bronchodilators before a walk	☐ Yes	☐ No	☐ NA
If yes, time it taken: ⌊⌊⌋:⌊⌊⌋			
The participant uses their usual walking aids during the test	☐ Yes	☐ No	☐ NA

For postbaseline 6MWTs: Has the participant used the same walking aid as in the first protocol-mandated 6MWT? ☐ Yes ☐ No ☐ NA *If the participant is on oxygen therapy, the flow rate must remain constant from 30 min prior to the 6MWT until the completion of the 6MWT. The way oxygen is delivered (delivery device, application route, way of carrying delivery device, flow rate) must be the same for all 6MWT assessments, unless a change is required for documented medical reasons.*

Performing the test	
Dyspnea using the Borg CR 10 Scale® *(before the 6MWT)* *(to be entered into the eCRF)*	
Total 6 Minute Walk Distance *(number of laps × length of each lap)* *+ final partial lap)* *(to be entered into the eCRF)*	meters
Was the 6MWT stopped before 6 minutes? (*If the participant stops walking to rest and then continues until the end of the 6 minutes, tick "No"*) *(to be entered into the eCRF)* *Note if the reason for stopping the 6MWT constitutes an AE, this is to be entered in the eCRF*	☐ No ☐ Yes If yes, ☐ PH related ☐ non-PH related
Dyspnea using the Borg CR 10 Scale® (*assessed immediately after the test*) *(to be entered into the eCRF)*	

After the test	
The corridor was kept clear during the 6MWT	☐ Yes ☐ No
Supplemental O2 given during the 6MWT *(if yes, the use of O2, and flow rate are to be entered into the concomitant therapy eCRF)*	☐ Yes ☐ No Flow rate: ⌊⌋⌋.⌊⌋ L/min
For participants on oxygen therapy, the flow rate remained constant from 30 min prior to the 6MWT until the completion of the assessment of dyspnea after the 6MWT	☐ Yes ☐ No If no, provide a comment below
Was the participant wearing a mask during the 6MWT?	☐ Yes ☐ No ☐ UNK
Comments (if applicable):	

Signature of the tester performing the 6MWT:	Signature of the staff member completing the worksheet (if different from the tester performing the 6MWT):
Date:	Date:

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Summary of changes for Amendment 2, 08 January 2021

Overall Rationale for the Amendment: The overall reasons for this protocol amendment are to provide clarification for several inclusion and exclusion criteria to better define the target population that may benefit from the study intervention, to add exploratory objectives and endpoints for long-term outcomes, to adapt to changed internal safety language and reporting processes, to align with TransCelerate template and to implement minor corrections and editorial revisions.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis - Safety evaluations; Section 8.4.3. Clinical Laboratory assessments	Serum pregnancy test *(not urine pregnancy test)* will be performed at End of treatment (EOT). "A serum pregnancy test will be performed at the site at screening **at Week 26 and at Week 52 (EOT)**; urine pregnancy tests will be performed at the site on Day 1 ~~and the EOT visit~~ and at the participant's home monthly between Day 1 and EOT and at End of Study (EOS), except for Month 6 and Month 12, when a serum pregnancy test is performed at the site visit (Week 26 and Week 52)."	Correction for consistency: Erroneous "urine" test at EOT. Should be serum test which is done by the central lab (corrected in Schedule of activities and in Section 8.4.3).
Section 1.1. Synopsis (Objectives/endpoints, Overall design); Section 1.2. Schema; Section 1.3. Schedule of Activities; Section 3. Objectives and Endpoints; Section 4.1. Overall Design; Section 6.2.2. Study Intervention Maintenance; Section 7.1. Discontinuation of Study Intervention	52-week assessment: Repetition of Week 26 assessments for exploratory objectives/endpoints at Week 52, except for Echo and Risk Assessment. EOT Week 52 Dispense/return of study drug at Weeks 26, 39, and 52 (return only).	Primary endpoint at Week 26 remains at Week 26. Exploratory endpoints at Week 52 or premature EOT to assess the sustainability of the Week 26 results.
Section 1.1. Synopsis - Exploratory Objectives; Section 3. Objectives and Endpoints	Additional exploratory objectives and exploratory endpoints are added. Objective: To assess the effects of selexipag on RV function using MRI at Week 52. Endpoint: Change from baseline to Week 52 assessed by MRI: RVSV, RVEDV, RVESV, RVEF, RV mass, RVGLS	Exploratory endpoints at Week 52 or premature EOT to assess the sustainability of the Week 26 results.
Section 1.1. Synopsis - Exploratory Objectives; Section 3. Objectives and Endpoints	Additional exploratory objectives and exploratory endpoints are added. Objective: To further assess the effects of selexipag on disease	Exploratory endpoints at Week 52 or premature EOT to assess the sustainability of the Week 26 results.

	severity and exercise capacity. Endpoint: Change from baseline to Week 52: WHO FC, NT-proBNP, 6MWD.	
Section 1.1. Synopsis - Exploratory Objectives; Section 3. Objectives and Endpoints	Additional exploratory objectives and exploratory endpoints are added. Objective: To evaluate the effect of selexipag on dyspnea during the 6-minute walking test (6MWT). Endpoint: Change from baseline in the difference between the pre-walk and post-walk assessed dyspnea Borg Dyspnea Index (BDI).	Participants may experience exercise induced dyspnea during the 6MWT. Dyspnea is an indicator of disease severity. The new objective and endpoint will evaluate the extent of dyspnea during the 6MWT.
Section 1.1. Synopsis- Exploratory Evaluations; Section 8.3.6. Biomarkers	Deletion of "The list of biomarkers may include: • Uric acid • Red cell distribution width • Activin A • Cystatin C • Follistatin • Galectin-3 • Growth differentiation factor-15 • Cardiac troponin T • Lactate dehydrogenase • Osteoprotegerin • Tumor necrosis factor alpha"	The biomarker samples will be analyzed based on the test results of previous studies and literature reports after the last participant has completed the study (last participant out). The current wording is not binding ("may") and therefore a general wording without specifying individual biomarkers is in-line with the current protocol.
Section 1.1. Synopsis; Section 8.6. Participant's Experience	Additional information was added regarding timing of assessment using EQ-5D-3L questionnaire and how health status as measured. Information regarding the prostacyclin associated AEs questionnaire was deleted.	The EQ-5D questionnaire was specified to mean EQ-5D-3L. Assessment at site visits was deemed sufficient. Therefore, EQ-5D-3L at the weekly phone calls during the titration period were removed. The prostacyclin questionnaire was removed since all AEs including those associated with prostacyclin are collected throughout the study at phone calls and site visits.
Section 1.1. Synopsis- Statistical Analyses; Section 9.4.1. General Considerations; Section 9.4.2. Primary Endpoints; Section 9.4.3. Secondary Endpoints	The statement was revised in Statistical Methods at relevant instances to include "World Health Organization (WHO) functional class (FC) (II/III) at baseline" instead of "pulmonary arterial hypertension (PAH) background therapy (yes/no)."	This reflects the new change for inclusion criteria 2 that specifies that enrollment will be stratified by proportion of FC II to FC III to approximately 40% and 60%, respectively.
Section 1.3. Schedule of Activities	The table was updated to clarify the study procedures and detailed information on visit names and time phase were added. • Clarification related to timepoints and visits are added for study periods: Up-titration to individual maintenance dose (IMD), Maintenance with IMD,	Clarity on number of site visits and adaptation to EOT at Week 52. Drug dispense/return visits were mentioned in the footnotes and easily missed. For clarity and completeness, drug dispense/return visits are now visible in the table.

	and Follow-up. • To align with the exploratory endpoints (Week 52), columns for site visits have been revised for study assessments/ evaluations.	
Section 1.3. Schedule of Activities	Following footnotes were updated. • Footnote "b": Participants must NOT take the morning study intervention dose before any visit-related procedure. ~~In case of premature EOT, the EOT visit should take place within 7 days after the decision to end treatment.~~ • Footnote "h": Urine pregnancy test at participant's home. The site will call female participants of childbearing potential monthly to check the pregnancy test result. **A window of ±5 days for each pregnancy test/phone call will be allowed.**	Foot notes were amended to accommodate the changes in the Table for clarity on number of site visits and adaptation to EOT at Week 52.
Section 1.3. Schedule of Activities	Footnotes "j" and "k" are deleted and further footnotes are renumbered. Following footnotes have been replaced to include updated information. • Footnote "l": ~~A telephone call will be made to the participant to monitor AEs, assess need for symptomatic treatment of side effects, decide dose for starting week, and document the participant's experience~~ **Only if EOT**. • Footnote "m": Participant's experience refers to ~~the prostacyclin associated AEs questionnaire (Section 10.7) and~~ the EQ-5D questionnaire (Section 10.~~7~~8).	Footnotes are renumbered/ repurposed. Foot notes were amended to accommodate the changes in the Table for clarity on number of site visits and adaptation to EOT at Week 52. Footnote "m": text referring to prostacyclin questionnaire was removed because the questionnaire will not be used.
Section 1.3. Schedule of Activities	Following new footnotes have been added in the table. • Footnote "o": If the results for the screening blood samples from the central laboratory are not available in time for Day 1 visit, an additional blood sample may be drawn to verify eligibility based on a local laboratory test. • Footnote "p": Including premature EOT. In case of	Foot notes were amended to accommodate the changes in the Table for clarity on number of site visits and adaptation to EOT at Week 52. • Footnote "o": To allow for merging the screening visit and Day 1 visit, all labs for eligibility can be done locally. • Footnote "p": To specify the assessments to be done in case of premature study intervention

	premature EOT, the EOT visit should take place within 7 days after the decision to end study intervention. • Footnote "q": Except for month of Week 26 and Week 52. • Footnote "r": In case of epidemic situation, eg, Corona Virus Disease-2019 (COVID-19), the Week 26 visit may be delayed up to an additional 28 days (Week 26 +6/-2 weeks).	discontinuation. • Footnote "q": To clarify that no phone calls are required when site visits are scheduled. • Footnote "r": The current window of the Week 26 visit is ±2 weeks. If a site- or participant-specific situation due to COVID-19 prevents the conduct of the Week 26 visit (primary efficacy endpoints) within the defined timeframe, the visit may be postponed by an additional 28 days resulting in a total time window of +6/-2 weeks. Accordingly, treatment with study intervention can be extended to avoid study intervention interruptions.
Section 1.3. Schedule of Activities	Monthly phone calls to monitor participant's safety during IMD maintenance phase are introduced.	Monthly phone calls from the site to the participant are introduced to monitor participant's safety by collecting information on concomitant medications, adverse events (AEs) and serious adverse events (SAEs).
Section 1.3. Schedule of Activities	Time window for telephone call visits was updated.	No time window defined in the current protocol. A window of ±3 days for the weekly phone calls during the titration phase and ±5 days for the phone calls during the IMD maintenance phase will be permitted to account for site or participant specific situations that prevent the phone call on the calculated date.
Section 1.3. Schedule of Activities	Expanded window for pregnancy tests done at home and associated phone calls.	No time window defined in the current protocol. A window of ±5 days for each pregnancy test/phone call will be allowed to account for site- or participant-specific situations that prevent the test/call on the calculated date. Allows for reminding the participant of the due date.
Section 4.1. Overall Design	Information in this section has been rearranged.	The flow of this section was rearranged to match the sequence of events. For completeness, weekly and monthly phone calls are described.
Section 4.2.1. Study Specific Ethical Design Considerations	Following sentence was revised. This is mitigated **assessing the primary endpoint after** a relatively short study duration and the permission to escalate PAH therapy **at any time** ~~if the investigator can~~	The mitigation of the primary ethical concern of a potential delay of study intervention escalation was modified to i) reflect the 52-week follow-up, and ii) to clarify that study intervention escalation is allowed at any time at the sole discretion of the

	~~justify, based on participant's symptoms, that it cannot be postponed to after Week 26 assessments~~.	investigator (no "justification" needed).
Section 5. Study Population	Additional details are added. To complement "**The local laboratory results (with the corresponding normal ranges) must be recorded in the electronic case report form (eCRF)**".	To include complementary information.
Section 5.1. Inclusion Criteria	Inclusion criterion 2 is modified. WHO FC II or III. **Enrollment will be stratified by WHO FC II to FC III. Proportion of participants with WHO FC II and WHO FC III are expected to be approximately 40% and 60%, respectively**.	The stratification by FC is to ensure that the majority of participants is at intermediate risk of disease progression.
Section 5.1. Inclusion Criteria	Inclusion criterion 3 is modified: PAH induced by drugs or toxins is added to the list of included PAH.	Drugs and toxins induced PAH is an etiology belonging to Group 1 pulmonary hypertension and has been included in previous studies with selexipag. Drugs and toxins induced PAH is included in an effort to align inclusion criteria with other selexipag studies allowing better comparability between them.
Section 5.1. Inclusion Criteria	Inclusion criterion 4 is modified: • Pulmonary vascular resistance (PVR) ~~>3 WU~~ **>5 Wood Unit (WU)** (400 dyn.s.cm^{-5}) • **Right ventricular stroke volume (RVSV) ≤60 mL as shown in right heart catheterization (Cardiac output [CO]/heart rate [HR]).**	The increase of the lower limit of PVR from >3 to >5 WU and introduction of RVSV threshold aim at enrolling a participant population with more advanced remodeling of the right ventricle.
Section 5.1. Inclusion Criteria	Inclusion criterion 5 is modified: **Patients already receiving PAH-specific oral mono or dual therapy (ie, phosphodiesterase type 5 inhibitors (PDE-5i) or soluble guanylate cyclase stimulators (sGCs) and/or ERA) or patients who are not candidates for these therapies. If on oral PAH-specific therapy, treatment has to be stable (ie, no introduction of new therapies or changes in dose) for at least 90 days prior to both ICF signature and Day 1.**	To clarify selection of participants according to the label indication of selexipag.
Section 5.1. Inclusion Criteria	Inclusion criterion 6 is modified: Correction of units for N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) levels.	The erroneous unit of NT-proBNP levels is changed to ng/L (from ng/mL). The range of NT-proBNP level

	NT-proBNP ~~>~~≥300 ng/~~m~~L at screening Added note: **If local assessment of BNP (instead of NT-proBNP) is used for eligibility, BNP measurement of ≥50 ng/L will be considered as meeting inclusion criterion.**	required for inclusion is adjusted to the ERS/ESC guidelines for intermediate risk: ≥300 ng/L (from >300 ng/L). To allow for merging the screening visit with the Day 1, local assessments of NT-proBNP or BNP (if BNP is measured routinely) are acceptable for inclusion.
Section 5.1. Inclusion Criteria	Inclusion criterion 7 is modified: Men or women ≥18 **years (or the legal age of consent in the jurisdiction in which the study is taking place if greater than 18)** and <65 years	In countries where the legal age to provide individual informed consent is greater than 18 years (eg, SOUTH KOREA), the participant population is restricted to participants who have reached this legal age.
Section 5.1. Inclusion Criteria	Inclusion criterion 8 is modified: • Agree to use reliable methods of contraception from Day 1 **for** at least 30 days after study intervention discontinuation (Section 10.5), and • Agree to perform monthly pregnancy tests ~~up to~~ **for** at least 30 days after study intervention discontinuation.	Contraception and pregnancy tests should be performed until at least 30 days after EOT.
Section 5.1. Inclusion Criteria	New inclusion criterion 9 is added: 6-minute walking distance (6MWD) ≥150 m during screening period.	Since FC IV participants are not eligible for this study, a 6MWD of <150 m may indicate a walking impairment not due to PAH and unlikely to improve with PAH treatment.
Section 5.2. Exclusion Criteria	Exclusion criterion 10 is modified. "Body mass index >40 kg/m^2 **or body weight <40 kg**"	Lower body weight limit to exclude participants with cachexia.
Section 5.2. Exclusion Criteria	Exclusion criterion 11 is modified: "Presence of one or more of the following signs of relevant lung disease at any time up to ~~screening~~ **Day 1** - if pulmonary function test results are missing, then exclusion 11 is considered as met**.**	Pulmonary function test results to assess the eligibility of a prospective study participant, can be part of the participant's medical history (historical data, no date restrictions) or when not available, pulmonary function testing can be performed after signing informed consent form and during the screening phase.
Section 5.2. Exclusion Criteria	Exclusion criterion 16 is modified: Removed "moderate" hepatic impairment as exclusion criterion. **Known and d**ocumented ~~moderate or~~ severe hepatic impairment (with or without cirrhosis) at screening, defined as Child-Pugh Class ~~B or~~ **C**. Added a foot note: **The assessment of hepatic impairment (Child-Pugh Score) must be fully documented for participants who**	Exclusion criterion aligned with the selexipag label. Exclusion criterion clarified to indicate that Child-Pugh scoring is only required in participants with hepatic impairment and does not apply to participants with no hepatic impairment.

	have clinical signs and/or evidence (from central and/or local lab) of hepatic impairment.	
Section 5.2. Exclusion Criteria	Exclusion criterion 22 is modified: Expanded to "**Pregnancy,** breastfeeding, **or intention to become pregnant during the study".**	To complement the criterion with important additional information in alignment with other sections of the protocol.
Section 5.4. Screen failures	Clarification on the rescreening process. ~~only screening assessments beyond the 28 day window will need to be repeated. Rescreened participants will be assigned a new participant number. The consent process will not be repeated when re screening participants.~~ **Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit to reassess eligibility during the screening period. If a participant does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the participant eligibility criteria, the participant may be rescreened on one occasion only. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.**	To adopt the wording from the TransCelerate template, clarifying the repetition of assessments during the screening period and the rescreening process.
Section 6.2. Study Intervention Administration	Following text added: "**Participants with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking (a) moderate cytochrome P450 (CYP)2C8 inhibitor(s) will start with 200 µg qd in the morning of Day 2".**	To complement the text including specific instructions for the administration of the study intervention in case of concomitant use of moderate CYP2C8 inhibitors or moderate hepatic impairment.
Section 6.2.1. Study Intervention Up-titration	Timing in the Table 2, Up-titration Guide is revised. Week: from 13-26 to 13-52 Days: from 85-182 to 85-364	To reflect the IMD duration now until EOT at Week 52.
Section 6.7. Study Intervention Dose Modification	Following text has been modified. ~~If~~ **For participants with moderate hepatic impairment (Child-Pugh B) or using** moderate inhibitors of CYP2C8 (eg, clopidogrel, deferasirox, teriflunomide, leflunomide) ~~are used~~	To complement the text including specific instructions for the administration of the study intervention in case of concomitant moderate hepatic impairment, concomitant use of strong inducers of CYP2C8, and concomitant use of

	concomitantly with **the** study intervention, dosing frequency of study intervention must be reduced to once a day. Text has been added regarding dose modification in case of concomitant use of strong inducers of CYP2C8 or strong inhibitors of UDP-glucuronosyltransferase (UGT)1A3 and UGT2B7. **It has been shown that, when moderate or strong inducers of CYP2C8 are used in combination with selexipag, the exposure to selexipag active metabolite is reduced by half. Dose adjustment of selexipag may be required with concomitant administration of inducers of CYP2C8 (eg, rifampicin, carbamazepine, phenytoin).** **The effect of strong inhibitors of UGT1A3 and UGT2B7 (eg, valproic acid, probenecid, and fluconazole) on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration may result in an increase in exposure to the active metabolite. Therefore, caution is required when these medicinal products are administered concomitantly with selexipag.**	strong inhibitors of UGT1A3 and UGT2B7, as per selexipag label.
Section 6.8. Continued Access to Study Intervention After the End of the Study	Title changed to "Continued Access to Study Intervention After the End of the Study" from "Intervention after end of the study". Following text added: **"If in the best interest of the study participant, commercial selexipag supply should start in the evening of EOT visit (date of last study medication dose) to avoid any unnecessary study intervention interruption."**	Heading text adjusted to match TransCelerate template. To complement the text including specific instructions for the administration of commercial selexipag after EOT.
Section 6.9. Overdose	Text moved from Section 8.6: Additional overdose definition included for participants with moderate hepatic impairment or concomitantly taking moderate CYP2C8 inhibitors which requires dosing frequency reduction from	Location of text adjusted to match TransCelerate template. Text adapted to match changes in internal safety reporting processes.

	bid to qd. Background information for overdose added.	
Section 7.1. Discontinuation of Study Intervention	Section was updated to: **The participant develops severe hepatic impairment. If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If a participant has developed severe hepatic impairment (Child-Pugh C) at any time during the study, the study intervention must be permanently discontinued (see Section 10.8).** ~~The participant develops (suspected) hepatic impairment. If hepatic impairment is suspected, a clinical assessment of severity (eg, Child Pugh score) should be performed. If a participant develops moderate or severe hepatic impairment (Child Pugh B or C) at any time during the study, the study intervention must be permanently discontinued.~~	Clarification to indicate that Child-Pugh scoring must be assessed and documented in case of hepatic impairment suspicion
Section 8. Study Assessments and Procedures	Total blood volume is revised from 27 mL to 69 mL. Table 3 has been revised for the volume of blood to be collected from each participant. Additional study specific materials added to the list.	Blood volume for Clinical Chemistry increased for the additional analysis of thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), and thyroxine (T4). Blood volume for Biomarkers increased from 2.5 mL to 10 mL to allow for more comprehensive tests as per laboratory instruction. Total blood volume increased due to the additional assessment at Week 52.
Section 8.3.1.5. Imaging Assessment	Following text was updated. After an individual participant's ~~EOT~~ **Week 26 or Week 52 imaging assessments**, a single reviewer will read all scans (MRI or Echo) of that participant at once.	Visits were updated to add more clarity about the timing of imaging assessments.
Section 8.3.2. 6MWT	Text as updated. Dyspnea will be assessed by the Borg CR 10 Scale®, a scale used to quantify the degree of shortness of breath **before and at the end of the 6MWT.**	Participants may experience exercise induced dyspnea during the 6MWT. Dyspnea is an indicator of disease severity. The new objective and endpoint will evaluate the extent of dyspnea during the 6MWT.
Section 8.4. Safety Assessments	New section (Section 8.4.2) is introduced to capture "Vital Signs". Added assessment of vital signs (HR, systolic blood pressure [SBP],	Vital signs are recorded for safety assessment in general and as part of risk mitigation strategy for adverse event of special interest (AESI).

	diastolic blood pressure [DBP]) during on-site visits	
Section 8.4.1. Physical Examination	Following text was modified. "Physical examination will include the evaluation of the participant's height (only at screening), ~~weight,~~ the general appearance, heart and lungs." Following statement was deleted from this section. "~~Body weight will be measured in indoor clothing without shoes.~~"	Body weight is being assessed as part of the newly added vital sign assessment (Section 8.4.2), and not as part of physical exam.
Section 8.4.2. Vital Signs	A new section is included.	The measurement of SBP, DBP, HR, and body weight was introduced as a measurement to monitor participant's safety during the study.
Section 8.4.3. Clinical Safety Laboratory Assessments; Section 10.2. Clinical Laboratory tests	The following text has been modified. Clinical chemistry panel **including TSH, T3, and T4** The following text has been removed from the table of Protocol-required Laboratory Assessments: ~~APTT, PT, INR~~	TSH, T3, and T4 included in the clinical chemistry laboratory assessment as part of risk mitigation strategy for AESI hyperthyroidism. Coagulation tests are needed to assess Child-Pugh score only when hepatic impairment is suspected. As this cannot be foreseen, these assessments will be done locally, when applicable, as defined in the corresponding sections.
Section 8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting	• The section heading was revised. • Text pertaining to safety reporting for the duration of study was modified.	To adapt the text to changes in internal safety reporting processes.
Section 8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Addition of Product Quality Complaints (PQC) to the safety reporting process. General updates related to the safety reporting process.	To adapt the text to changes in internal safety reporting. processes.
Section 8.5.2. Follow-up of Adverse Events and Serious Adverse Events	Updated information regarding the follow-up of adverse events.	To adapt the text to changes in internal safety reporting. processes.
Section 8.5.3. Regulatory Reporting Requirements for Serious Adverse Events	Updated information regarding reporting of suspected unexpected serious adverse events.	To adapt the text to changes in internal safety reporting processes.
Section 8.5.4. Pregnancy	Reference to faxing serious adverse events/pregnancy forms was replaced with "send". The name of the pregnancy form was updated to pregnancy notification form. Addition of pregnancy reporting for partners of male study participants.	To adapt the text to changes in internal safety reporting. processes.
Section 8.5.4. Pregnancy;	References to "Actelion Global	To adapt the text to changes in

Section 10.4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Drug Safety" references (or similar) were replaced by "Sponsor".	internal safety reporting processes.
Section 8.5.5. Disease-Related Events	This section was deleted.	To adapt the text to changes in internal safety reporting processes.
Section 10.2. Clinical Laboratory Tests	Following clinical chemistry parameter was added. **Glomerular filtration rate, using the Modification of Diet in Renal Disease (MDRD) formula**	To include assessment of kidney function by means of estimated glomerular filtration rate in a standardized way using the MDRD formula.
Section 10.4. Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Section heading was updated from "Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting" to "Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting".	Text adapted to match changes with the TransCelerate template.
Section 10.4. Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting – ATTRIBUTION DEFINITION	Text has been revised.	Text adapted to match changes with the TransCelerate template.
Section 10.4. Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting – ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS	Reference to disease-related events was removed.	To adapt the text to changes in internal safety reporting processes.
Section 10.4. Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting – SPECIAL REPORTING SITUATIONS	Addition of PQC to the special reporting situations.	To adapt the text to changes in internal safety reporting processes.
Section 10.4. Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting – PRODUCT QUALITY COMPLAINT HANDLING	Updated guidance on the handling of PQCs.	To adapt the text to changes in internal safety reporting processes.
Section 10.7. EuroQol 5-Dimension Questionnaire	Prostacyclin-associated adverse events questionnaire is deleted and	For completeness and reading convenience, the EQ-5D-3L

	a sample EQ-5D-3L questionnaire has been added.	questionnaire in English is presented in the appendix instead of the web-site reference only.
Section 10.8. Child-Pugh Classification	A new section is included.	To add Child-Pugh classification as reference to assess severity of liver impairment.
Section 10.9. 6-Minute Walk Test Guidance	Appendix 10.9 was replaced by the 6MWT guidance based on Sponsor's Template Version 3.3, dated 29 June 2020.	This is to align with updated Pulmonary Hypertension Therapeutic Area guidance document. Includes to add Borg's dyspnea assessment at the beginning of the 6MWT in addition to that assessed at the end of the 6MWT. The use of masks is described (and collected in the electronic case report form).
Section 11. References	Reference list was updated.	Added citations (literature references) to support the respective sections.
Throughout the protocol	References to "Actelion" were replaced by reference to "Sponsor". The term "subject" or "patient" was replaced with "participant". The term "study treatment" was replaced with "study intervention" for consistency.	To adapt the text to changes in internal safety reporting processes.
Throughout the protocol	New safety language	Safety language being updated to align with the Pulmonary Hypertension Therapeutic Area selexipag safety language implemented in all protocols. This includes the deletion of outdated safety contact numbers.
Throughout the protocol	Minor editorial revisions.	Minor errors were noted, and updates were made, wherever applicable.

COVID-19 Appendix (9 November 2020)

Overall Rationale: To provide a guidance on study conduct during the COVID-19 pandemic.

Summary of changes for Amendment 1, 20 February 2020

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.4.2 Clinical Safety Laboratory Assessments	Added that the site will call female participants of childbearing potential monthly to check the pregnancy test result.	Ensure pregnancy test result is regularly collected.
5.1 Inclusion Criteria	Added that females of childbearing potential who are only using a hormonal contraception method must have used it for at least 1 month (30 days) before Day 1 to be eligible.	Strengthen methods to avoid pregnancies in study participants.
10.5 Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Updated the table of examples of contraceptives.	Alignment with other studies.
5.3 Lifestyle Considerations	Added monthly pregnancy testing as an agreed requirement.	Clarification.
5.2 Exclusion criteria 6.6 Concomitant Therapy	Removed moderate inhibitors of CYP2C8.	Consistency with the current label, which indicates that moderate inhibitors of CYP2C8 are permitted.
6.6 Concomitant Therapy	Added that for PAH therapies to be initiated or up-titrated, documented symptoms resulting in the decision to escalate PAH treatment before Week 26 assessments were to be observed.	Clarification.
6.7 Study Intervention Dose Modification	Added clarification that if moderate inhibitors of CYP2C8 are used concomitantly with study intervention, then the dosing frequency of study intervention must be reduced to once a day. Dosing frequency of selexipag should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped.	Emphasized need for dose adjustment.
8.5.3 Regulatory Reporting Requirements for Serious Adverse Events	Deleted text referring to anticipated events.	The notion of "anticipated events" is not used.
8.3.2 6MWT	Removed text about use of 6MWT corridor card. Changed dyspnea assessment to Borg CR 10 Scale®.	Updated sponsor guidance for 6MWT.
10.6 Borg Dyspnea Index Scale	Deleted section.	Updated sponsor guidance for 6MWT.
10.9 Actelion 6MWT Guidance	Added section.	Updated sponsor guidance for 6MWT.
Synopsis	Changed the assessment of participant's experience (ie, prostacyclin-associated AEs questionnaire and the EQ-5D questionnaire) at screening to Day 1. Removed alternative therapies from mitigation strategies.	Clarification of timing and assessment.
1.2 Schema	Changed safety follow-up from 30 to 60 days to at least 30 days in schema for consistency with text.	Clarification of timing and assessment.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Added time window for return/dispensing visit.	Clarification of timing and assessment.
1.3 Schedule of activities	Deleted assessments related to participant experience at EOS.	Correction of timing and assessment.
1.3 Schedule of activities 3 Objectives and endpoints	Added footnote that participants' experience refers to the prostacyclin-associated AEs questionnaire and the EQ-5D questionnaire.	Clarification of timing and assessment.
1.3 Schedule of activities	Baseline participants' experience changed from screening to Day 1.	Clarification of timing and assessment.
1.3 Schedule of activities	Removed "of NT-proBNP" from footnote about eligibility based on blood laboratory results to make statement more general.	Clarification of timing and assessment.
1.3 Schedule of activities	Added "NT-proBNP" to footnote about safety-related and biomarker evaluations using blood draws.	Clarification of timing and assessment.
1.3 Schedule of activities	Added a footnote that study drug accountability will be performed once study drug has been returned after return/dispensing visits at end of Week 4 and end of Week 12.	Clarification of timing and assessment.
1.3 Schedule of activities	Added a footnote that participants must NOT take the morning study intervention dose before any visit-related procedure	Clarification of timing and assessment.
1.3 Schedule of activities	In case of premature EOT, the EOT visit should take place within 7 days after decision to end treatment.	Clarification of timing and assessment.
4.1 Overall Design	Added text to clarify that only screening assessments beyond the 28-day window will need to be repeated. Added text to clarify that the last study procedure to be performed on Day 1 will be selexipag intake.	Clarification of timing and assessment.
5.2 Exclusion Criteria	Added to criterion 18 that exceptions were elective hospitalizations for surgery or standard monitoring of pre-existing conditions that did not worsen.	Clarification of timing and assessment.
6.8 Intervention After EOS	Added the option that the participant's physician may request post-trial access to selexipag from the sponsor, based on favorable benefit/risk ratio for this specific participant.	Clarification.
7.3 Participant Discontinuation /Withdrawal from the Study	Added the word "only" to describe the options for reduced follow-up.	Clarification of assessment.
8.5 Adverse Events and Serious Adverse Events	Added "or last contact" to timeframe for duration of the study.	Clarification of timing.
8.7 Participant's Experience	Added that if an event meeting the definition of an AE is reported by a participant in the context of a questionnaire, it is the physician's responsibility to report it as an AE in the eCRF form.	Clarification of assessment.

Section Number and Name	Description of Change	Brief Rationale
	Changed the assessment of participant experience at screening to Day 1. Removed alternative therapies as a mitigation strategy.	
10.2. Clinical Laboratory Tests	Deleted 'and urine' from the pregnancy testing for women of childbearing potential because it will not be assessed by the central laboratory.	Clarification of assessment.
Protocol Title 1.1 Synopsis	Added study acronym, RESTORE.	Administrative.
Synopsis	Added the word "approximately" before the text about 80 participants to allow for variance.	Administrative.
5.4 Screen Failures	Consent process will not be repeated when re-screening participants, and rescreened participants should be assigned a new participant number.	Administrative.
6.1 Description of study intervention	Removed number of tablets per bottle to allow flexibility.	Administrative.
10.3 Regulatory, Ethical, and Study Oversight Considerations	Deleted text that the following documents must be provided to the sponsor before enrollment of the first participant: completed investigator financial disclosure forms from all subinvestigators and documentation of subinvestigator qualifications.	Administrative.
10.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added text on expected SAEs.	Administrative.
10.7 Prostacyclin-associated Adverse Events Questionnaire	Added participant number, date and time of questionnaire administration.	Administrative.
10.8 EuroQol 5-Dimension Questionnaire	Removed URL as vendor website has changed, and webpage no longer exists.	Administrative.
10.10 Protocol Amendment History	Updated with Amendment 1 information.	Administrative.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd. (a Janssen Pharmaceutical Company of Johnson & Johnson)

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	21-Apr-2022 12:15:18 (GMT)	Document Approval
PPD	21-Apr-2022 14:22:43 (GMT)	Document Approval