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

Clinical Protocol

Protocol Title

A Multicenter, Randomized, Double-blind, Placebo-controlled Study in Participants With Sarcoidosis-associated Pulmonary Hypertension (SAPH) to Assess the Efficacy and Safety of Oral Selexipag

SPHINX

Protocol AC-065D301; Phase 2
AMENDMENT 3

JNJ-67896049 / ACT-293987 (selexipag)

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	Date
Amendment 3	25-Feb-2022
Amendment 2	21-Sep-2020
Amendment 1	5-Dec-2019
Original Protocol	28-Mar-2019

Amendment 3 (25 February 2022)

Overall Rationale for the Amendment: The overall reason for Amendment 3 is to modify some inclusion and exclusion criteria aiming to facilitate enrollment (based on inputs from the Steering Committee [SC] of the SPHINX study), update Coronavirus Disease 2019 (COVID-19) appendix with recent updates pertaining to study conduct related to COVID-19 vaccine deployment for non-COVID-19 clinical trials, and implement miscellaneous minor corrections and clarifications.

A Protocol Amendment Summary of Changes Table for the current amendment is provided below. The updates are indicated in bold text and strike-through for the deleted text, wherever possible.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis (Objectives and Endpoints); 1.3.1. Visits and Assessments While Taking Study Intervention; 1.3.2. Visits and Assessments After Premature Discontinuation of Study Intervention; 3. Objectives and Endpoints; 8.2.2.5. Dyspnea (Pre- and Post-6MWT); 10.14. Appendix 14: Study Conduct During a Natural Disaster	Replaced Borg Dyspnea Index (BDI) with 'Borg CR Scale® (CR10)'.	For consistency with trade name.
1.3.2. Visits and Assessments After Premature Discontinuation of Study Intervention	Text updated to indicate that the survival follow-up to be conducted 'Yearly after study discontinuation until death or ±1 month of Visit 6 for the last participant **(EOMOP)**'.	For clarification.
4.2. Scientific Rationale for Study Design	Modified the terminology 'morbidity/mortality (M/M)' to 'clinical worsening'.	To align with the terminology of the corresponding efficacy endpoint.
1.1. Synopsis; 4.1. Overall Design; 4.4.1. EOS Visit	Sections updated and aligned with the revised definitions of 'end-of-study (EOS) Visit' under various circumstances for participant who complete or discontinue the treatment, before and after end-of-main-observation-period (EOMOP) or in case of entering the continued access program.	To align with the latest protocol template language.
5.1. Inclusion Criteria	Updated the reference supporting inclusion criterion # '4'	To rectify the error.
	Modified criterion # '9' with a note as follows:	An upper limit of the baseline 6-minute walk distance (6MWD)

	'6MWD ~~between~~ ≥50 ~~and 450~~ m both at Screening and at the time of randomization. **NOTE: Participants can use their usual walking aids during the test (e.g., cane, crutches). The same walking aid should be used for all 6MWTs. Walkers are not allowed.**'	is not regarded relevant. Added the note for clarification regarding the use of walking aids.
	Modified criterion # '10' as follows: '~~Forced vital capacity (FVC) >50% of predicted at Screening~~ **FVC >50% and FEV1 >50% of predicted at Screening**.'	Combination of the previous inclusion criteria # 10 and 11 into one.
	Modified criterion # '11' as follows: '~~FEV1/FVC ≥60%, or if FEV1/FVC <60% then FEV1 must be ≥60% of predicted at Screening~~ **DL_{CO} ≥40% of predicted. If DL_{CO} <40% of predicted, the extent of emphysema should not be greater than that of fibrosis as assessed by high resolution CT scan.**'	Addition of a diffusing capacity of the lung for carbon monoxide (DL_{CO}) criterion is deemed appropriate and useful, based on recent literature.
	Modified criterion # '14' as follows: 'A woman **only** using **hormonal** ~~oral~~ contraceptives must have been using this method for at least ~~1 month~~ **30 days** prior to randomization.'	For clarification.
5.2. Exclusion Criteria	Revised criterion # '8' as follow: '~~Implantable cardioverter defibrillator (ICD) for secondary prevention (current or planned)~~. **Participants who either are planning to receive an implantable cardioverter defibrillator (ICD) or who already have one that has delivered shock therapy any time in the previous 1 year prior to Day 1. Participants with ICD are eligible if no shock therapy has been delivered in the previous 1 year prior to Day 1**.'	As it is not required to exclude patients with an ICD if no shock therapy has been delivered 1 year prior to enrollment.
	Deleted criterion # '23': '~~Received an investigational intervention or used an invasive investigational medical device within 90 days prior to randomization.~~'	Content redundant with criterion # '22'.
	Modified criterion # '25' as follows: 'Any acute or chronic impairment that may influence the ability to comply with study requirements such as to perform RHC, a reliable and reproducible 6MWT ~~(eg, use of walking aids such as cane, walker, etc.),~~ or lung function tests.'	To be consistent with modified inclusion criterion # '9'.
6.1.3.1. Study Intervention Up-titration (previous)	Deleted section number and heading.	To remove redundancy.
8. Study Assessments and Procedures	Added new footnotes 'g' and 'h' to Table 2.	To clarify and align with Section 1.3.1.
	Revised 'Study-Specific Materials' with respect to pregnancy forms.	To update with latest available information.
8.2.2.1. Clinical Worsening and Hospitalization Related to PH-worsening	Deleted the phrase 'non-planned PH-related' associated with 'hospitalization'.	For accuracy.

10.5. Appendix 5: Contraceptive and Barrier Guidance	Updated the section heading and content.	To align with latest protocol template language.
10.14. Appendix 14: Study Conduct During a Natural Disaster (previously 'Appendix 14: COVID-19 Appendix')	Updated section heading and deleted the title page.	To align with latest protocol template.
	Section is updated with new pulmonary hypertension therapeutic area-specific standard text by Janssen.	To align with recent updates pertaining to study conduct related to COVID-19 vaccine deployment for non-COVID-19 clinical trials.
11. References	Updated the list of references and the citations throughout the document.	To align with organization's standard format of parenthetical referencing.
Throughout the protocol	• Replaced 'qd' with 'once daily' and 'bid' with 'twice daily'. • Corrected and updated references, as applicable. • Updated the abbreviations. • Minor corrections and editorial revisions are made.	For clarity and consistency.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Multicenter, Randomized, Double-blind, Placebo-controlled Study in Participants With Sarcoidosis-associated Pulmonary Hypertension (SAPH) to Assess the Efficacy and Safety of Oral Selexipag

Selexipag (JNJ-67896049 [also known as ACT-293987]) is a selective, orally available and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor), approved and commercially available for the treatment of patients with pulmonary arterial hypertension (PAH) in the United States (US), the European Union (EU), Japan, and other countries. Selexipag is currently being investigated for the treatment of sarcoidosis-associated pulmonary hypertension (SAPH), chronic thromboembolic pulmonary hypertension (CTEPH), arteriosclerosis obliterans (ASO) with intermittent claudication (IC), and lumbar spinal stenosis (LSS) with IC (IB selexipag).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effect of selexipag versus placebo on pulmonary vascular resistance (PVR) in participants with sarcoidosis associated pulmonary hypertension (SAPH) up to Week 26.	• PVR on study intervention up to Week 26 expressed as percent of the baseline value.
Exploratory	
• To evaluate the effect of selexipag versus placebo on time to clinical worsening (TTCW).	• TTCW up to end-of-main-observation-period (EOMOP) defined as at least one of the following components: All-cause death Unplanned pulmonary hypertension (PH)-related hospitalization Increase (ie, worsening) in WHO functional class (FC) Lung transplantation Atrial balloon septostomy Initiation of parenteral or new class of PH -specific therapy for clinical worsening
• To evaluate the effect of selexipag versus placebo on exercise capacity.	• Change from baseline in 6-minute walk distance (6MWD), Borg CR Scale® (CR10), oxygen saturation, and WHO FC at Week 39 and over time. • Proportion of participants with oxygen desaturation post-6-minute walk test (6MWT) at Week 39 and over time (identified by decrease in oxygen saturation [SpO^2] by at least 5% from pre-6MWT).

Objectives	Endpoints
• To evaluate the effect of selexipag vs placebo on daily life physical activity (DLPA) and sleep parameters.	• Change from baseline to Week 39 in actigraphy-assessed DLPA as measured by: Total DLPA in counts per minute Total volume of activity (above sedentary) Daily time spent (minutes) in non-sedentary activity Percentage of daily time spent in non-sedentary activity Moderate to vigorous physical activity (MVPA) Time spent in the different activity categories • Change from baseline to Week 39 in sleep parameters: Total sleep time (TST; minutes) Wake after sleep onset (WASO; minutes) Number of awakenings Sleep efficiency (percentage)
• To evaluate the effect of selexipag versus placebo on WHO FC.	• Proportion of participants with improvement, worsening and no change from baseline in WHO FC at Week 39 and over time.
• To evaluate the effect of selexipag versus placebo on death or PH-related hospitalizations.	• Rate of all-cause death or unplanned PH-related hospitalization up to EOMOP. • Time to all-cause death up to EOMOP.
• To evaluate the effect of selexipag versus placebo on patient-reported outcomes (PROs) assessed by the 12-Item Short Form Health Survey (SF-12), King's sarcoidosis questionnaire (KSQ), Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT), and Patient Global Assessment of Severity (PGA-S).	• Change from baseline up to Week 39 in SF-12 scores. • Change from baseline up to Week 39 in KSQ scores. • Change from baseline up to Week 39 in PAH-SYMPACT scores. • Change from baseline up to Week 39 in PGA-S scores.
• To evaluate the effect of selexipag versus placebo on clinician-reported outcomes (CROs) assessed by the Clinician Global Impression of Severity (CGI-S) and Clinician Global Impression of Change (CGI-C).	• Change from baseline up to Week 39 in CGI-S scores. • Change from baseline up to Week 39 as measured by CGI-C scores.
• To evaluate the effect of selexipag on the number of PH low-risk criteria.	• Absolute and change from baseline in the number of low-risk criteria based on WHO FC, 6MWD, N-

Objectives	Endpoints
	terminal pro B-type natriuretic peptide (NT-proBNP), and cardiac index (CIn) up to Week 26.
• To evaluate the effect of selexipag on NT-proBNP.	• Change from baseline in NT-proBNP serum levels up to Week 39.
• To evaluate the effect of selexipag on disease and pathway-related serum biomarkers.	• Change from baseline in serum biomarkers and associations between serum biomarker levels and clinical response and baseline characteristics up to Week 39.
• To evaluate the change in hemodynamic variables other than PVR	• Change from baseline in other hemodynamic variables (including cardiac output [CO], CIn, mean right atrial pressure [mRAP], mean pulmonary arterial pressure [mPAP], and mixed venous oxygen saturation [SVO_2]) up to Week 26.
Safety	
• To assess the overall safety of selexipag.	• Intervention-emergent adverse events (AEs). • Intervention-emergent prostacyclin-associated AEs. • Serious adverse events (SAEs) up to end-of-study (EOS). • AEs leading to premature discontinuation of study intervention. • Intervention-emergent AEs of special interest (eg, hypotension, anemia, hyperthyroidism). • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed timepoints during the study. • Intervention-emergent marked laboratory abnormalities. • Change from baseline in supplemental oxygen rate. • Change from baseline in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DL_{CO}). • Change from baseline in arterial blood gas parameters.

Hypothesis

The reduction in PVR after 26 weeks of treatment with selexipag is superior to placebo in participants with SAPH.

OVERALL DESIGN

This is a prospective, randomized, double-blind (DB), placebo-controlled, multicenter, interventional study in men and women ≥18 and ≤75 years of age with SAPH. Study intervention will be up-titrated to allow

each participant to reach their individual maximum tolerated dose (iMTD), in the range of 200 µg to 1,600 µg twice daily. For participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking a moderate cytochrome P450 (CYP)2C8 inhibitor(s) the dosing frequency is once daily.

The study starts with the first Informed Consent Form (ICF) signed by the first participant and ends with the last safety follow-up telephone call (TC) or visit of the last participant. The study comprises the following periods:

- A screening period of up to 30 days: starts with the signature of the ICF and ends with the participant's randomization at Visit 2, Day 1. The screening period should last at least 14 days to allow collection of baseline data for daily life physical activity (DLPA), sleep parameters, and Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™).
- Intervention and observation periods:

  A main observation period (MOP) that starts with the participants' randomization at Visit 2, Day 1 and with a titration phase of up to 12 weeks. Participants receive double-blind study intervention (selexipag or placebo) during this period. It ends on the day of the EOMOP visit. The EOMOP visit is the data cut-off for the primary efficacy and safety analyses. The EOMOP visit for all participants is planned at 39 Weeks ±1 month after randomization of the last participant. The duration of the MOP will be different for each individual participant and will depend on the time of each participant's individual date of randomization.

  - Participants who prematurely discontinue study intervention before the EOMOP visit will continue to perform visits and assessments as scheduled until the EOMOP visit.
  - For participants who prematurely discontinue study intervention before the EOMOP visit and who disagree to perform visits and assessments as scheduled until the EOMOP visit, long-term follow-up information regarding their survival status will be collected yearly until death or the time of EOMOP.
  - Information on the required procedures to follow if participants discontinue the study intervention prematurely is provided in Section 7.1.
- A DB extension period extending intervention for participants who do not prematurely discontinue study intervention before EOMOP: The period starts in the evening of the day of the EOMOP visit and ends with the end-of-treatment (EOT) visit. This period will last approximately 5 months. All participants entering the DB extension period will **continue** taking blinded study intervention (selexipag or placebo) during this period. Study intervention allocation will be unblinded approximately 1 month before the expected EOT visit.
- A safety follow-up period starting on the day after the last dose of study intervention and ending with the safety follow-up call at the End-of-Study (EOS) visit. For an individual participant, EOS visit is defined as follows:

  For participants who complete the treatment, EOS visit is defined as the safety follow-up visit (TC) 30 (+5) days after last dose of study intervention.

  For participants who prematurely discontinue study intervention for any reason before EOMOP visit (except for withdrawal from the study as defined in Section 7.2) but complete the main observation period (see Section 4.4.2), EOS visit corresponds to the last visit, which is either the EOMOP visit or the safety follow-up TC, whichever occurs last (see Schedule of Activities).

  For participants who prematurely discontinue study intervention for any reason before the EOMOP visit and who decline to continue with visits and assessments up to the EOMOP visit,

but agree to the collection of long-term survival information, the EOS visit corresponds to the last visit or TC before study discontinuation (see Schedule of Activities).

For participants who prematurely discontinue study intervention between the EOMOP and EOT visits for any reason (except for withdrawal from the study as defined in Section 7.2), the EOS visit corresponds to the safety follow-up TC (see Schedule of Activities).

For participants who complete the treatment and who are entering a continued access program (ie, other open-label extension study or post-trial access), the EOS visit is defined as the EOT visit and enrollment in the continued access program must occur on the day of the last visit in the SPHINX study.

A sponsor Data Monitoring Committee (DMC), Clinical Event Committee (CEC), and Steering Committee (SC) will be established.

The sponsor DMC has overall responsibility for safeguarding the interests of participants and will review safety data throughout the study. The sponsor DMC will provide recommendations to the study team.

The CEC will be a sub-committee of the SC that will review and adjudicate the following cases: hospitalization, WHO FC increase (ie, worsening), and initiation of PH-specific therapy.

An SC is involved in the study design and will provide guidance on the study conduct and study publications.

The EOS at study level is considered as the last visit or safety follow-up TC, whichever occurs last, for the last participant in the study.

NUMBER OF PARTICIPANTS

Approximately 74 participants will be randomized in a 1:1 ratio to receive either selexipag or placebo. Randomization will be stratified by PH-specific therapies at baseline (yes *vs* no).

INTERVENTION GROUPS AND DURATION

Study Participation Duration

The duration of individual participation in the study will be different for each individual participant (between approximately 15 months and up to approximately 3.5 years) and will depend on the time of each participant's individual date of entry into the study and the total recruitment time.

Description of Interventions

Selexipag 200 µg and matching placebo, will be provided as oral tablets in childproof bottles. Study intervention will be up-titrated to allow each participant to reach their iMTD, in the range of 200 µg to 1,600 µg (ie, 1 to 8 tablets). Dosing frequency will be twice daily, except for participants with moderate hepatic impairment (Child-Pugh Class B), or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s), who receive study intervention once daily.

Each participant will start with 1 tablet of study intervention, ie, selexipag (200 µg) or matching placebo, in the evening of Day 1, and will continue with 200 µg twice daily on Day 2. Participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s) will start with 200 µg once daily in the morning of Day 2. The dose will be up-titrated by the investigator/delegate in 200 µg twice daily/once daily increments at weekly intervals during scheduled TCs until reaching the iMTD (see table below). If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to 2 weeks. If needed, the dose can be reduced by 200 µg twice daily/once daily. The decision to not further up-titrate the dose will be based on the investigator's medical judgment based on the occurrence and severity of

typical pharmacological effects of IP receptor agonists and the participant's individual tolerability. At Week 12 (Visit 3), the twice daily/once daily dose reached for each participant is defined as the iMTD. This dose must be kept stable at least until Week 39 (Visit 6) but can be adjusted for safety and tolerability reasons.

Any study intervention interruption of 3 days or more will require a new up-titration.

Study intervention interruptions exceeding 14 consecutive days must lead to permanent discontinuation of study intervention.

Study Intervention Up-titration Scheme

Period	Dose regimen	Duration	
First dose	200 µg	On Day 1 in the evening (pm)	1 tablet
Up titration	200 µg twice daily *, §	From Day 2 am to Day 8 am**	1 tablet twice daily §
	400 µg twice daily*, §	From Day 8 pm to Day 15 am**	2 tablets twice daily §
	600 µg twice daily*, §	From Day 15 pm to Day 22 am**	3 tablets twice daily §
	800 µg twice daily*, §	From Day 22 pm to Week 4 am**	4 tablets twice daily §
	1,000 µg twice daily*, §	From Week 4 pm to Week 5 am**	5 tablets twice daily §
	1,200 µg twice daily*, §	From Week 5 pm to Week 6 am**	6 tablets twice daily §
	1,400 µg twice daily*, §	From Week 6 pm to Week 7 am**	7 tablets twice daily §
	1,600 µg twice daily*, §	From Week 7 pm to Week 12 am**	8 tablets twice daily §
Maintenance	iMTD: 200 µg to 1,600 µg twice daily §	From Week 12 onwards	1 8 tablets twice daily §

am morning;; iMTD individual maximum tolerated dose; pm evening.
* Or the iMTD until Week 12.
** If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to 2 weeks.
§ For participants with moderate hepatic impairment (Child Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s) the dosing frequency is once daily. These participants must take the study intervention in the morning; hence the first dose of study intervention should be taken in the morning of Day 2.

EFFICACY EVALUATIONS

The efficacy assessments include, but are not limited to, PVR up to Week 26, assessment of exercise capacity, dyspnea, and WHO FC, measurement of the NT-proBNP levels, and recording PROs and CROs.

SAFETY EVALUATIONS

Safety and tolerability assessments include review of concomitant medications and AEs, clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, physical examination, pulmonary function tests, DL_{CO}, oxygen saturation and pregnancy testing.

STATISTICAL METHODS

Analysis Timepoints

There are 2 Analysis Timepoints:

- Analysis Timepoint 1 (final analysis for the primary endpoint and all supportive efficacy endpoints): When all participants have completed the EOMOP visit, or survival information is available (or if participants have discontinued the study prematurely). At this timepoint, the primary analysis of the PVR endpoint will be conducted. Data for all remaining endpoints will also be analyzed. After the database lock for the main observation period is done, the study team will be unblinded.
- Analysis Timepoint 2 (additional follow-up): When all participants have completed the study (EOS) or discontinued prematurely. At this timepoint, the additional safety data collected during the DB extension period will be reported.

Sample Size Calculation

The calculation of sample size was approximated by Z-test for superiority on the log-transformed ratio of PVR to baseline at Week 26 (or premature EOT if study intervention is discontinued before Week 26) using the software package EAST™ version 6.4.0.1 for difference of means. A total sample size of 74 participants will provide a power of 90% for the treatment effect of a 30% relative decrease (ie, improvement) in geometric mean (GM) as compared to placebo, with a CV of 0.5 and a 2-sided significance level of 0.05.

Primary Efficacy Analysis

The derived parameter that will be used for the primary efficacy analysis is the ratio of the PVR value postintervention initiation up to Week 26, ie, at Week 26 or at premature EOT in case of discontinuation of study intervention before Week 26 (post) vs the PVR value pre-intervention initiation at baseline (pre), expressed as a percentage, ie:

$$\text{PVR post to pre percent} = \left(\frac{\text{PVR at Week 26 (or premature EOT)}}{\text{PVR at baseline}}\right) \times 100\ (\%)$$

Missing PVR assessments at baseline or post-baseline will be imputed specific to the reason for missing data (refer to statistical analysis plan [SAP] for more details).

As a summary measure, ratio of the GM of the *PVR post to pre percent* between selexipag and placebo, obtained by exponentiation of the difference in means of the natural logarithm transformed *PVR post to pre percent* between selexipag and placebo will be calculated, ie:

$$\frac{\text{GM(PVR post to pre percent in selexipag)}}{\text{GM(PVR post to pre percent in placebo)}}$$

The analyses of the primary efficacy endpoint will be tested using the ANCOVA model.

From the ANCOVA model, *PVR post to pre percent* will be summarized by intervention group using covariate adjusted GM and corresponding 2-sided 95% CI. The between-group ratio of GM with corresponding 95% 2-sided CI and p-value will be displayed as the placebo-corrected intervention effect.

For each intervention group, the least square mean and 2-sided 95% CI of the natural logarithm of the *PVR post to pre percent* will be inversely transformed using the exponential function and multiplied by 100 to provide the GM of the *PVR post to pre percent* and the corresponding 2-sided 95% CI, expressed as a percentage.

Absolute values at baseline and post-baseline as well as absolute pre-post changes from baseline to postbaseline in PVR will be summarized using descriptive statistics.

Other Exploratory Efficacy Analysis

For continuous and categorical endpoints, where applicable, the response profiles over time (eg change from baseline, proportions of participants by categorical endpoint categories) will be inspected graphically and by the usual summary statistics at each visit (with 95% CI) up to the EOMOP visit by randomized treatment group on the randomized set (RS). Two sets of profiles will be provided: one considering assessments measured on study intervention up to the EOMOP visit, and one including all data collected up to the EOMOP visit, regardless of treatment discontinuations.

Time-to-event endpoints will be analyzed using the Kaplan-Meier method by randomized treatment group up to EOMOP regardless of study intervention discontinuations.

Safety Analysis

For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

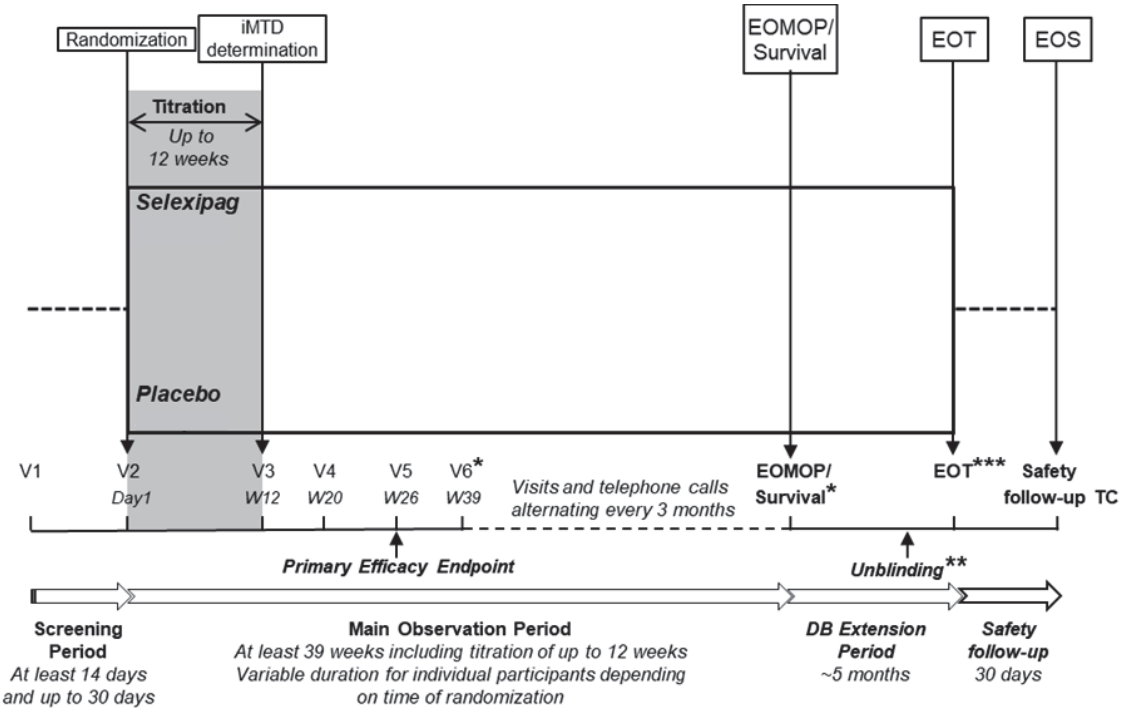
Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint by intervention group. Frequency tabulations of abnormalities will be made.

Descriptive statistics of pulse rate, systolic and diastolic blood pressure (SBP and DBP, respectively) values and changes from baseline will be summarized at each scheduled timepoint by intervention group.

Descriptive statistics of values and changes from baseline in supplemental oxygen rate, PFTs and blood gas analysis will be summarized by intervention group.

1.2. Schema

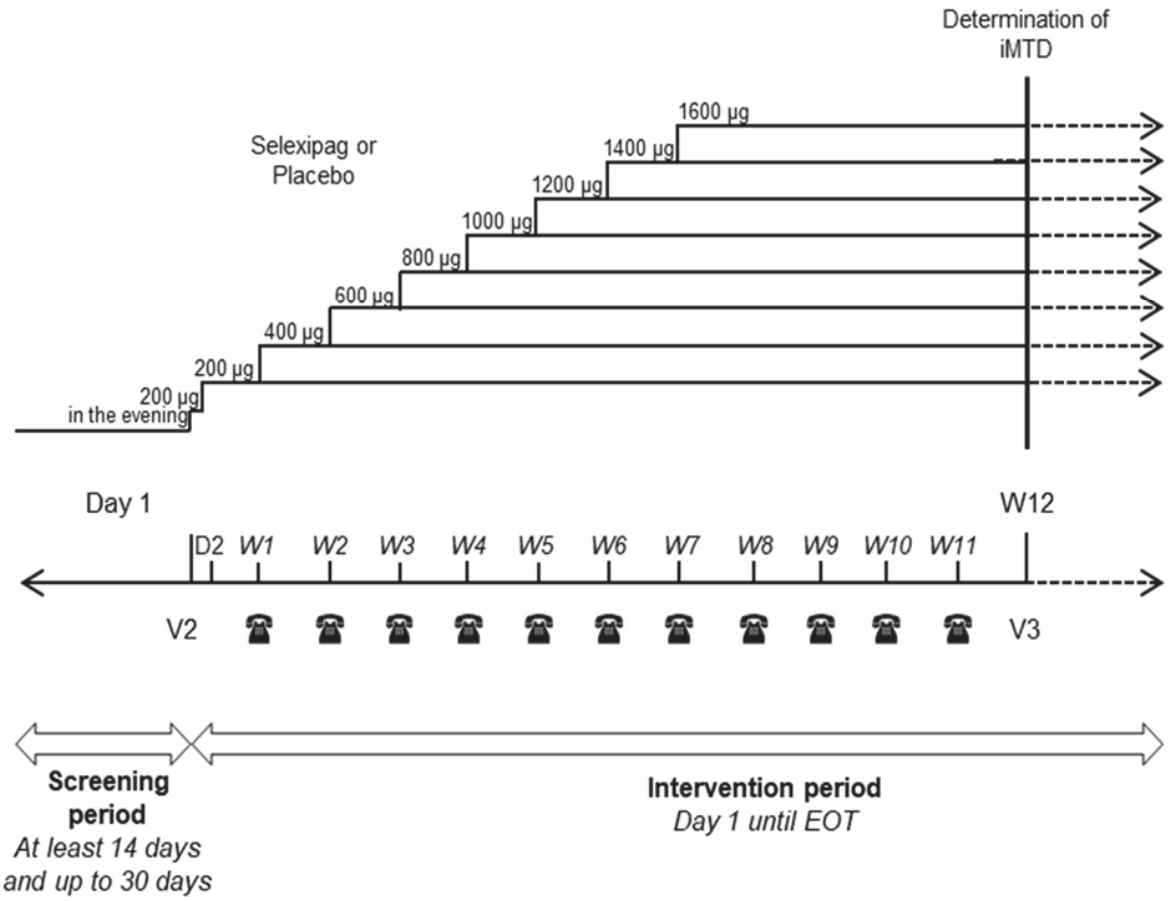
Figure 1: Schematic Overview of the Study



EOMOP end of main observation period; EOS end of study; EOT end of treatment; iMTD individual maximum tolerated dose; TC telephone call, V visit; W week.

*The EOMOP visit has to be performed within ±1 month of planned Visit 6/ Week 39 of the last participant and it will be announced approximately 9 months in advance. For the last participant, the EOMOP visit will be the Visit 6/Week 39. For all other participants, if the EOMOP visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated. Survival information will be collected for participants who discontinued from study intervention and visits and assessments.
**Intervention group allocation will be provided to study sites approximately 1 month prior to EOT.
***Study intervention will be provided until the EOT visit, which is planned approximately 5 months after the last EOMOP visit. In case of premature discontinuation of study intervention, the premature EOT visit should be performed within 7 days after last study intervention dose and participants should continue to perform visits and assessments up to the EOMOP visit.

Figure 2: Titration Phase Design



D day; EOT end of treatment; iMTD individual maximum tolerated dose; V visit; W week.

NOTE: In general, dosing frequency will be twice daily, except for participants with moderate hepatic impairment (Child Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s), for whom the dosing frequency is to be reduced to once daily. These participants must take the study intervention in the morning, hence the first dose of study intervention should be taken in the morning of Day 2.

1.3. Schedule of Activities

1.3.1. Visits and Assessments While Taking Study Intervention

PERIODS	NAME	SCREENING	MAIN OBSERVATION PERIOD on-treatment (on double-blind study intervention)									DB EXTENSION PERIOD	SAFETY FOLLOW-UP	
VISITS	Number	1	2	Weekly TC	3	4	5	6	TC every 6 months	Visit every 6 months	EOMOP	EOT	Safety follow-up TC	U1, 2, 3, etc.
	Name	Screening	Randomization	Titration Phase (W1, W2, W3, etc.)	Week 12	Week 20	Week 26	Week 39	Week 52, 78, 104, etc.	Week 65, 91, 117, etc.	EOMOP [a]	EOT	Safety follow-up TC	Unscheduled visit [b]
	Time	Day 30 to Day 1	Day 1	Day 8 (±3 days) and weekly (±3 days) until Day 78 (± 3 days)	Day 85 (±7 days)	Day 141 (±7 days)	Day 183 (±7 days)	Day 274 (±7 days)	Day 365, 547, 729, etc. (±7 days)	Day 456, 638, 819, etc. (±7 days)	Announced (within ±1 months of the planned Visit 6 for the last participant)	Announced (approximately 5 months after EOMOP)	30 (+5) days after EOT	Any time
Screening/Administrative														
Informed consent (ICF) [d]		X												
Optional biomarker ICF		X												
Demographics and height		X												
Review medical history requirements		X												
Inclusion/exclusion criteria		X	X [n]											
Prestudy therapy		X	X											
Serum pregnancy test (WOCBP) [e; f]		X												
Urine pregnancy test (WOCBP) [g]			X	monthly (±7 days)									X	
Study Intervention Administration														
Randomization			X											
Study intervention dispensing/return			X		X	X	X	X		X	X	X		
Study intervention administration [h]			X	X	X	X	X	X	X	X	X			
Efficacy Evaluations														
RHC		X [i]					X [j]							
6MWT/Borg CR Scale® (CR10)/SpO_2		X	X		X [k]	X [k]	X [k]	X [k]		X [k]	X [k]	X [k]		X [c; k]
WHO FC		X	X		X	X	X	X		X	X	X		X [c]
Actigraphy [f]		X [l]			X	X	X	X						

PERIODS	NAME	SCREENING	MAIN OBSERVATION PERIOD on-treatment (on double-blind study intervention)									DB EXTENSION PERIOD	SAFETY FOLLOW-UP	
VISITS	Number	1	2	Weekly TC	3	4	5	6	TC every 6 months	Visit every 6 months	EOMOP	EOT	Safety follow-up TC	U1, 2, 3, etc.
	Name	Screening	Randomization	Titration Phase (W1, W2, W3, etc.)	Week 12	Week 20	Week 26	Week 39	Week 52, 78, 104, etc.	Week 65, 91, 117, etc.	EOMOP [a]	EOT	Safety follow-up TC	Unscheduled visit [b]
	Time	Day 30 to Day 1	Day 1	Day 8 (±3 days) and weekly (±3 days) until Day 78 (± 3 days)	Day 85 (±7 days)	Day 141 (±7 days)	Day 183 (±7 days)	Day 274 (±7 days)	Day 365, 547, 729, etc. (±7 days)	Day 456, 638, 819, etc. (±7 days)	Announced (within ±1 months of the planned Visit 6 for the last participant)	Announced (approximately 5 months after EOMOP)	30 (+5) days after EOT	Any time
SF 12 [f], King's SQ [f], PGA S [f]		X			X	X	X	X						
PAH SYMPACT™ [f]		X [m]			X	X	X	X						
CGI S [f]		X			X	X	X	X						
CGI C [f]					X	X	X	X						
NT proBNP [f]			X		X	X	X	X						
Safety Evaluations														
Vital signs (BP, HR), weight		X	X		X	X	X	X		X	X	X		X [c]
Local 12 lead ECG (single)		X						X				X		
Physical examination [g]		X					X			X		X		X [c]
Arterial Blood Gas (ABG)		X [o]					X [p]							
DL_{CO}		X					X					X		
Spirometry		X					X					X		
Clinical Laboratory Tests														
Hematology, clinical chemistry [f]		X	X		X	X	X	X		X	X	X		
Biomarkers														
Serum and plasma samples for exploratory biomarker research [f, r]			X		X		X	X						
Ongoing Participant Review														
Concomitant Therapy				X	X	X	X	X	X	X	X	X		X [c]
SAEs/AEs [q]		X	X	X	X	X	X	X	X	X	X	X	X	X [c]

6MWT = 6-minute walk test; ABG = Arterial Blood Gas; AE = adverse event; BP = blood pressure; CGI-S = Clinician Global Impression of Severity; CGI-C = Clinician Global Impression of Change; DB = double-blind; DL_{CO} = diffusing capacity of the lung for carbon monoxide; ECG = electrocardiogram; EOMOP = end-of-main-observation-period; EOT = end of treatment; eCRF = electronic Case Report Form; FC = functional class; HR = heart rate; ICF = informed consent form; King's SQ = King's sarcoidosis questionnaire; NTproBNP = N terminal pro b-type natriuretic peptide; O = optional; PAH = pulmonary arterial hypertension; PAH-SYMPACT™ = pulmonary arterial hypertension-symptoms and impact; PGA-S = Patient Global

Assessment of Severity; PH = pulmonary hypertension; RHC = right heart catheterization; SAE = serious adverse event; SF-12 = 12-Item Short Form Health Survey; SpO_2 = peripheral capillary oxygen saturation; TC = telephone call; WHO = World Health Organization; WOCBP = woman of childbearing potential.

a. The EOMOP visit will have to be performed within ± 1 month of the planned Visit 6/Week 39 of the last participant and will be announced approximately 9 months in advance. For the last participant the EOMOP visit will be Visit 6/Week 39. For all other participants, if the EOMOP visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated.
b. Unscheduled visits may be performed at any time during the study. Assessments (other than reporting of AE/SAE and concomitant medication) are to be performed at the discretion of the investigator and are reported in the eCRF. An unscheduled visit must be performed for reasons outlined in Section 8. Footnote c indicates which assessments are mandatory in case an unscheduled visit is performed for reasons outlined in Section 8.
c. In case an unscheduled visit is performed for reasons outlined in Section 8, this assessment must be performed and recorded in the eCRF.
d. Must be signed before first study-related activity.
e. A serum pregnancy test must be performed at Screening or in case of a positive urine pregnancy test.
f. Transferred electronically by an external service provider.
g. Assessment not collected in eCRF.
h. In case of twice daily dosing, first dose to be taken in the evening of Day 1. In case of once daily dosing, the first dose of study intervention should be taken in the morning of Day 2. Includes study intervention up-titration (see Section 6.1.3 for detailed information).
i. A historical RHC is allowed taking into account the restrictions provided in Section 8.2.1.1.1. If no historical results are available, an RHC must be performed during the Screening period only if all other inclusion criteria are met and none of the exclusion criteria is met.
j. If the 6MWT and RHC are assessed on the same day the RHC should be performed after the 6MWT and within 2 to 5 hours post-dose.
k. To be performed within 2 to 5 hours post-dose and prior to the RHC (if applicable).
l. To collect baseline data, participants should wear the actigraphy device 14 days between Visit 1 (Screening) and Visit 2 (Randomization). It is recommended to start on the day following the screening visit. If required, the baseline RHC should not be done during this time.
m. To assess baseline, the PAH-SYMPACT™ questionnaire should be completed on 7 consecutive days starting on the day following the screening visit. If required, the baseline RHC should not be done during the 7 consecutive days of the PAH-SYMPACT completion.
n. If the results for the screening blood samples from the central laboratory are not available in time for randomization of the participant, an additional blood sample may be drawn to verify eligibility based on a local laboratory test.
o. A historical ABG is allowed taking into account the restrictions provided in Section 8.3.6. If no historical results are available, an ABG must be performed during the Screening period.
p. The ABG can be done during the RHC taking into account the restrictions provided in Section 8.3.6.
q. All AE and SAEs will be reported throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) or death or lost to follow-up (see Section 7.3).
r. Optional assessment.

1.3.2. Visits and Assessments After Premature Discontinuation of Study Intervention

PERIODS	NAME	SAFETY FOLLOW-UP		MAIN OBSERVATION PERIOD off-treatment (after premature discontinuation of double-blind study intervention)								SURVIVAL FOLLOW-UP
VISITS	Number	Premature EOT	Safety follow-up TC	3	4	5	6	TC every 6 months	Visit every 6 months	EOMOP	U1, 2, 3, etc.	SFU 1, 2, 3, etc.
	Name	Premature EOT [a]	Safety follow-up TC	Week 12	Week 20	Week 26	Week 39	Week 52, 78, 104, etc.	Week 65, 91, 117, etc.	EOMOP [b]	Unscheduled visit [c]	Survival follow-up [e]
	Time	Within 7 days after last study intervention dose	30 (+5) days after last study intervention dose	Day 85 (±7 days)	Day 141 (±7 days)	Day 183 (±7 days)	Day 274 (±7 days)	Day 365, 547, 729, etc. (±7 days)	Day 456, 638, 819, etc. (±7 days)	Announced (within ±1 month of the planned Visit 6 for the last participant)	Any time	Yearly after study discontinuation until death or ±1 month of Visit 6 for the last participant (EOMOP)
Screening/Administrative												
Serum pregnancy test (WOCBP) [f, g]												
Urine pregnancy test (WOCBP) [h]		X	X									
Study Intervention Administration												
Study intervention dispensing/return		X										
Efficacy Evaluations												
RHC		X [j, i]										
6MWT / Borg CR Scale® (CR10) /SpO_2		X		X	X	X	X		X	X	X [d]	
WHO FC		X		X	X	X	X		X	X	X [d]	
Actigraphy [g; l]		X		X	X	X	X					
SF 12 [g; l], King's SQ [g; l], PGA S [g; l]		X		X	X	X	X					
PAH SYMPACT™ [g; l]		X		X	X	X	X					
CGI S [g; l]		X		X	X	X	X					
CGI C [g; l]		X		X	X	X	X					

PERIODS	NAME	SAFETY FOLLOW-UP		MAIN OBSERVATION PERIOD off-treatment (after premature discontinuation of double-blind study intervention)								SURVIVAL FOLLOW-UP
VISITS	Number	Premature EOT	Safety follow-up TC	3	4	5	6	TC every 6 months	Visit every 6 months	EOMOP	U1, 2, 3, etc.	SFU 1, 2, 3, etc.
	Name	Premature EOT [a]	Safety follow-up TC	Week 12	Week 20	Week 26	Week 39	Week 52, 78, 104, etc.	Week 65, 91, 117, etc.	EOMOP [b]	Unscheduled visit [c]	Survival follow-up [e]
	Time	Within 7 days after last study intervention dose	30 (+5) days after last study intervention dose	Day 85 (±7 days)	Day 141 (±7 days)	Day 183 (±7 days)	Day 274 (±7 days)	Day 365, 547, 729, etc. (±7 days)	Day 456, 638, 819, etc. (±7 days)	Announced (within ±1 month of the planned Visit 6 for the last participant)	Any time	Yearly after study discontinuation until death or ±1 month of Visit 6 for the last participant (EOMOP)
NT pro BNP [g, l]		X		X	X	X	X					
Safety Evaluations												
Vital signs (BP, HR), weight		X		X	X	X	X		X	X	X [d]	
Local 12 lead ECG (single)		X					X					
Physical examination [h]		X				X			X		X [d]	
Arterial Blood Gas (ABG)		X [k]										
DL_{CO}		X				X						
Spirometry		X				X						
Clinical Laboratory Tests												
Hematology, clinical chemistry [g]		X		X	X	X	X		X	X		
Biomarkers												
Serum and plasma samples for exploratory biomarker research [g, n, l]		X										
Ongoing Participant Review												
Concomitant Therapy		X		X	X	X	X	X	X	X	X [d]	
SAEs/AEs [m]		X	X	X	X	X	X	X	X	X	X [d]	
Survival [e]												X

6MWT = 6-minute walk test; ABG = Arterial Blood Gas; AE = adverse event; BP = blood pressure; CGI-S = Clinician Global Impression of Severity; CGI-C = Clinician Global Impression of Change; DB = double-blind; DL_{CO} = diffusing capacity of the lung for carbon monoxide; ECG = electrocardiogram; EOMOP = end-of-main-observation-period; EOT = end-of-treatment; eCRF = electronic Case Report Form; FC = functional class; HR = heart rate; ICF = informed consent form; King's SQ = King's sarcoidosis questionnaire; NT-proBNP = N-terminal pro b-type natriuretic peptide; O = optional; PAH = pulmonary arterial hypertension; PAH-SYMPACT™ = pulmonary arterial hypertension-symptoms and impact; PGA-S = Patient Global Assessment of Severity; PH = pulmonary hypertension; RHC = right heart catheterization; SAE = serious adverse event; SF-12 = 12-Item Short Form Health Survey; SpO_2 = peripheral capillary oxygen saturation; TC = telephone call; WHO = World Health Organization; WOCBP = woman of childbearing potential.

a. Participants who discontinue study intervention and have their premature EOT visit before the EOMOP visit will continue with visits and assessments until the EOMOP visit. If the premature EOT visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated.
b. The EOMOP visit will have to be performed within ± 1 month of the planned Visit 6/Week 39 of the last participant and will be announced approximately 9 months in advance. For the last participant the EOMOP Visit will be Visit 6/Week 39. For all other participants, if the EOMOP visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated.
c. Unscheduled visits may be performed at any time during the study. Assessments (other than reporting of AE/SAE and concomitant medication) are to be performed at the discretion of the investigator and are reported in the eCRF. An unscheduled visit must be performed for reasons outlined in Section 8. Footnote d indicates which assessments are mandatory in case an unscheduled visit is performed for reasons outlined in Section 8.
d. In case an unscheduled visit is performed for reasons outlined in Section 8, this assessment must be performed and recorded in the eCRF.
e. Only for participants who prematurely discontinue from study intervention and who disagree to continue to perform visits and assessments until EOMOP, survival information will be collected yearly (Section 8.2.2.2).
f. A serum pregnancy test must be performed in case of a positive urine pregnancy test.
g. Transferred electronically by an external service provider.
h. Assessment not collected in eCRF.
i. In case of premature discontinuation of study intervention before Visit 5/Week 26 it is recommended to perform a postbaseline RHC and within 3 days after last dose of study intervention and before initiation of new PH-specific therapies if possible.
j. If the 6MWT and RHC are assessed on the same day the RHC should be performed after the 6MWT.
k. ABG is only mandatory at the premature EOT in case of premature discontinuation before Visit 5/Week 26 and can be done during the RHC taking into account the restrictions provided in Section 8.3.6.
l. This assessment can only be done at the premature EOT in case of premature discontinuation of study intervention before Visit 6/Week 39.
m. All AE and SAEs will be reported throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) or death or lost to follow-up (see Section 7.3)
n. Optional assessment.

2. INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological disorder that may involve multiple clinical conditions and can complicate several cardiovascular and respiratory diseases such as left ventricular dysfunction and chronic obstructive pulmonary disease.

Sarcoidosis is a multisystemic disorder that is characterized by non-caseating granulomas which are present in multiple tissues, particularly in the lung and lymphatic system. Pulmonary hypertension (PH; defined as a mean pulmonary artery pressure [PAP] of ≥25 mm Hg at rest measured by right heart catheterization [RHC]) is increasingly recognized as a serious complication of pulmonary sarcoidosis and is associated with an increased morbidity and mortality (Baughman 2010, 2011; Huitema 2016; Kirkil 2018; Shorr 2003; Shlobin 2014). The World Health Organization (WHO) generally classifies sarcoidosis -associated PH (SAPH) as Group 5 ie, PH with an unknown and multifactorial mechanism (Galiè 2016; Ryan 2012). Severe untreated PH carries a poor prognosis and is associated with higher mortality in patients with interstitial lung diseases and sarcoidosis. Early diagnosis and consideration of treatment options may be key for improving patient outcomes (Diaz-Guzman 2008). There are no clear data regarding the true prevalence of SAPH. The proportion of sarcoidosis patients with PH varies from 5% to 20 % (Huitema 2016).

While there is no approved treatment for SAPH, PH-specific treatments are frequently used, including endothelin receptor antagonists (ERA; eg, bosentan, ambrisentan, macitentan), phosphodiesterase type-5 inhibitors (PDE5i; eg, sildenafil), guanylate cyclase agonist (eg, riociguat), and prostacyclin analogues (eg, i.v. epoprostenol or inhaled iloprost) (Shlobin 2014). There is evidence from small studies and case series that PH-specific therapies reduce pulmonary vascular resistance (PVR) and impact other pulmonary hemodynamic parameters in patients with SAPH. Some of these studies also showed an improvement in WHO functional class (FC), exercise capacity, or Quality of Life (QoL) (Barnett 2009; Baughman 2009, 2014; FDA Guidance 2003).

Selexipag (JNJ-67896049 [also known as ACT-293987]) is a selective, orally available and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor), approved and commercially available for the treatment of patients with pulmonary arterial hypertension (PAH) in the United States (US), the European Union (EU), Japan, and other countries. Selexipag is currently being investigated for the treatment of SAPH, chronic thromboembolic pulmonary hypertension (CTEPH), arteriosclerosis obliterans (ASO) with intermittent claudication (IC), and lumbar spinal stenosis (LSS) with IC (IB selexipag).

The term “study intervention” throughout the protocol, refers to study drug (selexipag or placebo).

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.

The term “participant” throughout the protocol refers to the common term “subject”.

2.1. Study Rationale

The rationale for this study is based on the unmet medical need for new therapeutic options for patients with SAPH and is supported by the established efficacy and safety of selexipag in the PAH indication, the shared pathomechanism between SAPH and PAH, and the available data on the efficacy and safety of PH-specific therapies in SAPH.

This study will be the first global, randomized, controlled study to explore the efficacy and safety of selexipag for the treatment of SAPH. The purpose of this study is to assess the efficacy and safety of selexipag in the studied population.

2.2. Background

For the most recent comprehensive quality, nonclinical, and clinical information, refer to the latest version of the Investigator's Brochure for selexipag (IB selexipag).

2.3. Benefit/Risk Assessment

2.3.1. Known Benefits

The clinical benefits of selexipag for the treatment of SAPH have yet to be established.

2.3.2. Potential Benefits

Efficacy of selexipag in the treatment of adult patients with symptomatic PAH was demonstrated in the AC-065A302 (GRIPHON) study, a large (N 1,156) randomized long-term, controlled morbidity/mortality study (Noel 2017; Sitbon 2015). 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 WHO FC II III and was fully preserved in patients already treated with an approved PAH-specific medicine at baseline (80% of the study population), as well as in patients 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, in which the mean duration of treatment was nearly 1.5 years (and up to 4.2 years). 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 pathological 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 (Galiè 2016).

Given the pathophysiological and clinical similarities between SAPH and PAH, SAPH patients may benefit from selexipag treatment.

2.3.3. Known Risks

The safety and tolerability of selexipag in patients with SAPH has not yet been evaluated.

2.3.4. Potential Risks

The tolerability and safety profile of selexipag administered to SAPH patients is expected to be consistent with that in adult patients with PAH.

The short- and long-term safety profile of selexipag has been established in PAH patients in the AC-065A302 (GRIPHON) study conducted in 1,156 participants and is mainly characterized by prostacyclin-associated adverse events (AEs) associated 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 reactions, reflecting the mode of action of selexipag, included headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing.

Other AEs reported more frequently on selexipag compared to placebo 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 patients had systolic blood pressure (SBP) <90 mm Hg on at least 1 occasion, compared to 6.7% in the placebo group. A decrease from baseline of >40 mm Hg in SBP was reported for 2.3% and 3.0% of patients in the selexipag and placebo groups, respectively.

Sinus tachycardia was reported more frequently on 12-lead electrocardiogram (ECG) with selexipag compared to placebo.

Hyperthyroidism was reported more frequently in the selexipag group compared to the placebo group. Corresponding laboratory changes were a small reduction in thyroid stimulating hormone (TSH) at most post-baseline visits.

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

2.3.5. Overall Benefit/Risk Assessment

The overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- Efficacy and safety of selexipag has been established in the PAH indication.
- There is an unmet medical need for therapeutic options for patients with SAPH.
- Given the pathophysiological and clinical similarities between SAPH and PAH, it is anticipated that SAPH patients could benefit from selexipag treatment.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) 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:

- In general, safety evaluations (including but not limited to thyroid function tests, blood pressure monitoring, hematology laboratory tests) will be performed at scheduled visits during the study, as indicated in the Schedule of Activities.
- The investigator or the designee will document unsolicited AEs as indicated in Section 10.4.
- Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable condition is reached.

Safety measures are included in this protocol to minimize the potential risk to participants, including the following:

- Participants will discontinue study intervention for the reasons included in Section 7.1.
- The study will be closely monitored by a sponsor Data Monitoring Committee (DMC) throughout its conduct.

It is the investigator's responsibility to monitor the individual benefit/risk 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 he/she believes that continuation would be detrimental to the participant's well-being.

More detailed information about the known and expected benefits and risks of selexipag may be found in the latest version of the Investigator's Brochure (IB selexipag) and in local Product Information.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effect of selexipag versus placebo on pulmonary vascular resistance (PVR) in participants with sarcoidosis associated pulmonary hypertension (SAPH) up to Week 26.	• PVR on study intervention up to Week 26 expressed as percent of the baseline value.
Exploratory	
• To evaluate the effect of selexipag versus placebo on time to clinical worsening (TTCW).	• TTCW up to end-of-main-observation-period (EOMOP) defined as at least one of the following components: All-cause death Unplanned PH-related hospitalization Increase (ie, worsening) in WHO functional class (FC) Lung transplantation

Objectives	Endpoints
	Atrial balloon septostomy Initiation of parenteral or new class of PH-specific therapy for clinical worsening
• To evaluate the effect of selexipag versus placebo on exercise capacity.	• Change from baseline in 6-minute walk distance (6MWD), Borg CR Scale® (CR10), oxygen saturation, and WHO FC at Week 39 and over time. • Proportion of participants with oxygen desaturation post 6-minute walk test (6MWT) at Week 39 and over time (identified by decrease in oxygen saturation [SpO2] by at least 5% from pre-6MWT).
• To evaluate the effect of selexipag vs placebo on daily life physical activity (DLPA) and sleep parameters.	• Change from baseline to Week 39 in actigraphy-assessed DLPA as measured by: Total DLPA in counts per minute Total volume of activity (above sedentary) Daily time spent (minutes) in non-sedentary activity Percentage of daily time spent in non-sedentary activity Moderate to vigorous physical activity (MVPA) Time spent in the different activity categories • Change from baseline to Week 39 in sleep parameters: Total sleep time (TST; minutes) Wake after sleep onset (WASO; minutes) Number of awakenings Sleep efficiency (percentage)
• To evaluate the effect of selexipag versus placebo on WHO FC.	• Proportion of participants with improvement, worsening and no change from baseline in WHO FC at Week 39 and over time.
• To evaluate the effect of selexipag versus placebo on death or PH-related hospitalizations.	• Rate of all-cause death or unplanned PH-related hospitalization up to EOMOP. • Time to all-cause death up to EOMOP.

Objectives	Endpoints
• To evaluate the effect of selexipag versus placebo on patient-reported outcomes (PROs) assessed by the 12-Item Short Form Health Survey (SF-12), King's sarcoidosis questionnaire (KSQ), Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT), and Patient Global Assessment of Severity (PGA-S).	• Change from baseline up to Week 39 in SF-12 scores. • Change from baseline up to Week 39 in KSQ scores. • Change from baseline up to Week 39 in PAH-SYMPACT scores. • Change from baseline up to Week 39 in PGA-S scores.
• To evaluate the effect of selexipag versus placebo on clinician-reported outcomes (CROs) assessed by the Clinician Global Impression of Severity (CGI-S) and Clinician Global Impression of Change (CGI-C).	• Change from baseline up to Week 39 in CGI-S scores. • Change from baseline up to Week 39 as measured by CGI-C scores.
• To evaluate the effect of selexipag on the number of PH low-risk criteria.	• Absolute and change from baseline in the number of low-risk criteria based on WHO FC, 6MWD, N-terminal pro B-type natriuretic peptide (NT-proBNP), and Cardiac Index (CIn) up to Week 26.
• To evaluate the effect of selexipag on NT-proBNP.	• Change from baseline in NT-proBNP serum levels up to Week 39.
• To evaluate the effect of selexipag on disease and pathway-related serum biomarkers.	• Change from baseline in serum biomarkers and associations between serum biomarker levels and clinical response and baseline characteristics up to Week 39.
• To evaluate the change in hemodynamic variables other than PVR.	• Change from baseline in other hemodynamic variables (including cardiac output [CO], CIn, mean right atrial pressure [mRAP], mean pulmonary arterial pressure [mPAP], and mixed venous oxygen saturation [SVO_2]) up to Week 26.
Safety	
• To assess the overall safety of selexipag.	• Intervention-emergent AEs. • Intervention-emergent prostacyclin-associated AEs. • Serious adverse events (SAEs) up to end-of-study (EOS). • AEs leading to premature discontinuation of study intervention.

Objectives	Endpoints
	• Intervention-emergent AEs of special interest (eg, hypotension, anemia, hyperthyroidism). • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed timepoints during the study. • Intervention-emergent marked laboratory abnormalities. • Change from baseline in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DL_{CO}). • Change from baseline in supplemental oxygen rate. • Change from baseline in arterial blood gas parameters.

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

The reduction in PVR after 26 weeks of treatment with selexipag is superior to placebo in participants with SAPH.

4. STUDY DESIGN

4.1. Overall Design

This is a prospective, randomized, double-blind (DB), placebo-controlled, multicenter, interventional study in men and women ≥18 and ≤75 years of age with SAPH. Study intervention will be up-titrated to allow each participant to reach their individual maximum tolerated dose (iMTD), in the range of 200 µg to 1,600 µg twice daily. For participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate cytochrome P450 (CYP)2C8 inhibitor(s) the dosing frequency is once daily. Diagrams of the study design and titration are provided in Figure 1 and Figure 2, respectively.

Approximately 74 participants will be randomized in a 1:1 ratio to receive either selexipag or placebo. Randomization will be stratified by PH-specific therapies at baseline (yes *vs* no).

The study starts with the first informed consent form (ICF) signed by the first participant and ends with the last safety follow-up telephone call (TC) or visit of the last participant. The study comprises the following periods:

- A screening period of up to 30 days: starts with the signature of the ICF and ends with the participant's randomization at Visit 2, Day 1. The screening period should last at least 14 days to allow collection of baseline data for daily life physical activity (DLPA), sleep parameters and PAH- SYMPACT™ (Section 10.7).

- Intervention and observation periods:

  A main observation period (MOP) which starts with the participants randomization at Visit 2, Day 1 and with a titration phase of up to 12 weeks. Participants receive double-blind study intervention (selexipag or placebo) during this period. It ends on the day of the EOMOP visit. The EOMOP visit is the data cut-off for the primary efficacy and safety analyses. The EOMOP visit for all participants is planned 39 Weeks ±1 month after randomization of the last participant. The duration of the MOP will be different for each individual participant and will depend on the time of each participant's individual date of randomization.

  - Participants who prematurely discontinue study intervention before the EOMOP visit will continue to perform visits and assessments as scheduled until the EOMOP visit (see Section 1.3.2).
  - For participants who prematurely discontinue study intervention before the EOMOP visit and who disagree to perform visits and assessments as scheduled until the EOMOP visit long-term -follow-up information regarding their survival status will be collected yearly until death or the time of EOMOP.
  - Information on the required procedures to follow if participants discontinue the study intervention prematurely is provided in Section 1.3.2 and Section 7.1.

  – A DB extension period extending intervention for participants who do not prematurely discontinue study intervention before EOMOP. The period starts in the evening of the day of the EOMOP visit and ends with the end-of-treatment (EOT) visit. This period will last approximately 5 months. All participants entering the DB extension period will continue taking study intervention (selexipag or placebo) during this period. Study intervention allocation will be unblinded approximately 1 month before the expected EOT visit. The EOT visit may be performed at any time during the 1 month following unblinding.

- A safety follow-up period starting on the day after the last dose of study intervention and ending with the safety follow-up call at the EOS visit. For an individual participant, EOS visit is defined as follows:

  For participants who complete the treatment, EOS visit is defined as the safety follow-up visit (TC) 30 (+5) days after last dose of study intervention.

  For participants who prematurely discontinue study intervention for any reason before EOMOP visit (except for withdrawal from the study as defined in Section 7.2) but complete the main observation period (see Section 4.4.2), EOS visit corresponds to the last visit, which is either the EOMOP visit or the safety follow-up TC, whichever occurs last (see Schedule of Activities).

  For participants who prematurely discontinue study intervention for any reason before the EOMOP visit and who decline to continue with visits and assessments up to the EOMOP visit, but agree to the collection of long-term survival information, the EOS visit corresponds to the last visit or TC before study discontinuation (see Schedule of Activities).

For participants who prematurely discontinue study intervention between the EOMOP and EOT visits for any reason (except for withdrawal from the study as defined in Section 7.2), the EOS visit corresponds to the safety follow-up TC (see Schedule of Activities).

For participants who complete the treatment and who are entering a continued access program (ie, other open-label extension study or post-trial access), the EOS visit is defined as the EOT visit and enrollment in the continued access program must occur on the day of the last visit in the SPHINX study.

The duration of individual participation in the study will be different for each participant (between approximately 15 months and up to approximately 3.5 years), and will depend on the time of each participant's individual date of entry into the study and the total recruitment time.

The visit schedule and protocol-mandated procedures are performed according to the Schedule of Activities.

The efficacy assessments include, but are not limited to, RHC at Week 26, assessment of exercise capacity, dyspnea, WHO FC, measurement of the NT-proBNP levels, recording PROs and CROs. Refer to Section 8.2 for more information.

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) or date of last contact (see Section 7.3). Safety and tolerability assessments include review of concomitant medications and AEs, clinical laboratory tests, ECG, vital signs, physical examination, pulmonary function tests, DL_{CO}, oxygen saturation and pregnancy testing. Refer to Section 8.3 and Section 8.3.5 for more information.

Plasma and serum samples will be collected and archived for future analysis of disease or pathway-related biomarkers. Refer to Section 8.5 for more information.

There are two Analysis Timepoints (see Section 9.3 for detailed information):

- Analysis Timepoint 1 (final analysis for the primary endpoint and all supportive efficacy endpoints): When all participants have completed the EOMOP visit, or survival information is available (or if participants have discontinued the study prematurely). At this timepoint, the primary analysis of the PVR endpoint will be conducted. Data for all other endpoints will also be analyzed. After the database lock for the MOP is done, the study team will be unblinded.
- Analysis Timepoint 2 (additional follow-up): When all participants have completed the study (EOS) or discontinued the study prematurely. At this timepoint, the additional safety data collected during the DB extension period will be reported.

A sponsor DMC, SC and CEC will be established (see Section 10.3).

The sponsor DMC has overall responsibility for safeguarding the interests of participants and will review safety data throughout the study (see Section 9.6). The sponsor DMC will provide recommendations to the study team.

An SC is involved in the study design and will provide guidance on the study conduct and study publications. Refer to Section 10.3 Appendix 3 for more information.

The CEC will be a sub-committee of the SC that will review and adjudicate the following cases: hospitalization, WHO FC increase (ie, worsening), and initiation of PH-specific therapy. Refer to Section 10.3 for more information. A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Rationale for the Use of Placebo/Randomization/Stratification/Blinding

A placebo-controlled study conducted in a randomized and DB fashion will be used to evaluate the efficacy of selexipag and will allow to establish the frequency and magnitude of changes in hemodynamic and clinical endpoints that may occur in the absence of active intervention. The use of a placebo control will also allow proper evaluation of any safety related events or abnormalities and disease progression observed during the study and to differentiate between events potentially related to the use of selexipag vs those related to the underlying disease.

A placebo-controlled study is considered ethically acceptable due to the lack of approved treatment for SAPH. The use of background therapy with PH-specific therapies (excluding prostanoids, prostacyclin analogues and non-prostanoid IP receptor agonists) is allowed. In addition, treatment escalation of PH-specific therapies is allowed following the Week 39 visit (Visit 6). Stable treatment for sarcoidosis is also allowed.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups.

Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Randomization will be stratified by PH-specific therapies at baseline (yes *vs* no) to enhance the validity of statistical comparisons across intervention groups and to account for a potentially different treatment effect in participants already receiving PH-specific therapies compared to treatment-naïve participants.

Rationale for the Duration of the Study

Participants will receive DB selexipag or placebo until EOT. PVR and other hemodynamic endpoints will be assessed by RHC at Week 26, which is considered sufficient to observe hemodynamic changes. Other clinical endpoints, eg, exercise capacity and PROs will be assessed up to Week 39, and TTCW and rate of hospitalization related to PH-worsening or death will be assessed up to EOMOP.

The total duration of the study of approximately 3.5 years with variable follow-up time for individual participants is expected to allow for an evaluation of the TTCW endpoint and the long-term safety and tolerability endpoints in a blinded fashion.

In order to be able to estimate the effect of treatment initially assigned at baseline, regardless of adherence to the planned course of treatment (intent-to-treat principle), participants who prematurely discontinue the study intervention will be followed up until EOMOP.

Continued treatment with blinded study intervention for approximately 5 months beyond the EOMOP visit until the study results are available will allow investigators to make an informed decision on post-study therapy based on the primary analysis results and the actual intervention received by the study participants.

Rationale for the Study Population

There is currently no approved treatment for SAPH. SAPH is a serious complication of sarcoidosis and is associated with increased morbidity and mortality (clinical worsening), particularly in precapillary SAPH. Given the evidence from small studies and case studies that PH-specific therapies reduce PVR and impact other pulmonary hemodynamic variables in patients with precapillary SAPH, the demonstrated efficacy of selexipag in clinical worsening risk reduction in PAH, and the hemodynamic similarities between PAH and precapillary SAPH, selexipag may represent a potential treatment option for this patient population.

Rationale for Right Heart Catherization

Precapillary PH is characterized by an increased resistance to blood flow in the pulmonary vasculature quantified by PVR. PVR is determined by RHC. Since this procedure is indispensable for the diagnosis of PH and to evaluate treatment response (Galiè 2016), sites treating PH patients are well experienced with RHC. The study will include sites that are specialized in treating PH patients and performing RHC. The risk associated with RHC procedures is considered acceptable for this study as it is reported to be low in centers experienced in treating PH patients and performing RHC (Hoeper 2006). In addition, a historical RHC is allowed for all participants if it was performed in accordance with the guidance provided in Section 8.2.1.1.

Rationale for the Primary Endpoint

The choice of PVR as the primary endpoint in this study is based on the prognostic and predictive value of PVR for clinical outcome in PH and the similarities between precapillary SAPH and PAH.

Rationale for Optional Biomarker Collection

Optional biomarker samples will be collected for exploratory biomarker analyses to evaluate the biology of SAPH and pulmonary fibrosis, to discover markers of disease severity, to provide a biological assessment of the response of participants to treatment with selexipag, to analyze differences between responders and non-responders, and to determine if markers can be used to classify participants as potential responders prior to treatment. The samples may also be used to develop tests/assays related to selexipag, SAPH and/or pulmonary fibrosis.

Analyses of biomarkers may be performed at the sponsor's discretion and reported separately from this study.

No human deoxyribonucleic acid (DNA) analyses will be performed on these samples.

4.2.1. Study-Specific Ethical Design Considerations

In the continuing search for efficacious and safe medications, thorough scientific evaluation of any intervention is an ethical requirement before exposing the target population. This study is being conducted to evaluate the efficacy and safety of selexipag in participants with SAPH.

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. They will be informed 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.

There are no specific ethical concerns. The following ethical aspects have been considered: the study is conducted in a DB fashion using a placebo control group, and PVR is assessed by an invasive method, RHC. The rationale for these ethical aspects is addressed above.

The measures that are taken to minimize the risks for participants are described in Section 2.3.5.

The total blood volume to be collected from the population over the study period (see Table 2) is considered to be acceptable based upon WHO recommendations (WHO Guidelines 1994).

4.3. Justification for Dose

Study intervention will be up-titrated (see Section 6.1.3) to allow each participant to reach their iMTD, in the range of 200 µg to 1,600 µg twice daily; or in the range of 200 µg to 1,600 µg once daily for participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s). This is in accordance with the approved regimen and doses per local Product Information. Depending on the iMTD, a single dose of study intervention will consist of 1 to 8 tablets (200 µg to 1,600 µg).

4.4. End-of-Study Definition

4.4.1. EOS Visit

Refer to Section 4.1 for EOS visit definition for individual participants in various scenarios.

4.4.2. Participant Completion

A participant will be considered to have completed **the study** if he or she has completed the main observation period (ie, visits and assessments up to and including the EOMOP visit), whether or not on study intervention. Participants who prematurely discontinue study intervention and withdraw from the study (see Section 7.2) will be considered to have not completed the study.

4.4.3. Study Completion

Sites will be informed once the enrollment for the study is completed, ie, last planned participant randomized.

All ongoing participants, whether or not on study intervention, should be invited to perform their EOMOP visit (39 weeks [±1 month] after randomization of the last participant).

Final survival information will be collected for participants who prematurely discontinued from the study except for the reason 'withdrawal of consent' (39 weeks [±1 month] after randomization of the last participant).

The End-of-Study (EOS) at a study level is considered as the last visit or safety follow-up TC (see Section 4.4.1), whichever occurs last, 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 visit/TC at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 30 days. The screening period should start at least 14 days before administration of study intervention to allow for collection of baseline DLPA, sleep parameters, and pulmonary arterial hypertension-symptoms and impact (PAH-SYMPACT™) data.

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.

It is the responsibility of the investigator/delegate to obtain written informed consent from each subject participating in this study after adequate face-to-face explanation of the objectives, methods, and potential hazards of the study. The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure. See Section 10.3 for more information.

Participants who are in Screening when the enrollment target has been met may still be randomized.

For a discussion of the statistical considerations of participant selection, refer to Section 9.4, Sample Size Determination.

5.1. Inclusion Criteria

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

1. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

2. Male or female.

3. 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 75 years of age, inclusive, at Screening.

4. Confirmed diagnosis of sarcoidosis as per American Thoracic Society (ATS) criteria (Crouser 2020; Statement on sarcoidosis 1999).

5. Sarcoidosis-associated precapillary PH, confirmed by RHC (at rest) within 90 days prior to randomization:
   a. PVR ≥320 dyn*sec/cm^5 (≥4.0 Wood units)
   b. Mean pulmonary arterial pressure (mPAP) ≥25 mm Hg
   c. Pulmonary artery wedge pressure (PAWP) ≤15 mm Hg, or if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) ≤15 mm Hg.

   Note: A historical RHC is allowed taking into account the restrictions provided in Section 8.2.1.1. If no historical results are available, an RHC must be performed during the Screening period, but only if all other inclusion criteria are met and none of the exclusion criteria is met.

6. PH severity according to modified WHO FC II IV at Screening and randomization; participants in WHO FC IV must be in a stable condition and able to perform a 6MWT.

7. Criterion modified per Amendment 2

   7.1 Either not receiving PH-specific treatment, or receiving PH-specific oral monotherapy (ie, riociguat or PDE5i or ERA); if on oral PH-specific monotherapy treatment has to be stable (ie, no introduction of new therapies or changes in dose) for at least 90 days prior to both the RHC qualifying for enrollment and randomization.

8. Criterion modified per Amendment 2

   8.1 Stable sarcoidosis treatment regimen, ie, no new specific anti-inflammatory treatment for sarcoidosis for at least 90 days, and stable dose(s) for at least 30 days prior to both the RHC qualifying for enrollment and randomization.

9. Criterion modified per Amendment 3

   9.1 6MWD ≥50 m both at Screening and at the time of randomization.

   NOTE: Participants can use their usual walking aids during the test (eg, cane, crutches). The same walking aid should be used for all 6MWTs. Walkers are not allowed.

10. Criterion modified per Amendment 3

    10.1 FVC >50% and FEV_1 >50% of predicted at Screening.

    NOTE: Short-acting-beta-agonists (eg, salbutamol) and long-acting-beta-agonists must not be taken 6 hours and 24 hours prior to spirometry testing, respectively.

11. Criterion modified per Amendment 3

    11.1 DL_{CO} ≥40% of predicted. If DL_{CO} <40% of predicted, the extent of emphysema should not be greater than that of fibrosis as assessed by high resolution CT scan.

    NOTE: Short-acting-beta-agonists (eg, salbutamol) and long-acting-beta-agonists must not be taken 6 hours and 24 hours prior to spirometry testing, respectively.

12. For patients enrolled or planned to be enrolled in a cardio-pulmonary rehabilitation program based on exercise training, one of the following must apply:

    - In the maintenance phase of the program at the time of randomization with no plans to stop the program until Week 39, or
    - Start of the cardio-pulmonary rehabilitation program based on exercise training is planned after Week 39.

13. A woman must be (as defined in Section 10.5)

    a. Not of childbearing potential
    b. Of childbearing potential and
        - Have a negative highly sensitive serum β-human chorionic gonadotropin (β-hCG) at Screening and a negative urine pregnancy test at randomization.
        - Agree to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study intervention discontinuation.
        - Practicing an acceptable method of contraception and agreeing to remain on an acceptable method while receiving study intervention and until 30 days after last dose of study intervention. Examples of acceptable methods of contraception are located in Section 10.5.

14. Criterion modified per Amendment 3:

    14.1 A woman only using hormonal contraceptives must have been using this method for at least 30 days prior to randomization.

15. Willing and able to adhere to the lifestyle restrictions specified in Section 5.3.

5.2. Exclusion Criteria

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

1. PH due to left heart disease (PAWP >15 mm Hg).
2. PH due to compression of pulmonary arteries and/or pulmonary veins.
3. History of left heart failure (LHF) as assessed by the investigator including cardiomyopathies and cardiac sarcoidosis with a left ventricular ejection fraction (LVEF) <40%.
4. Severe coronary heart disease (CHD) or unstable angina as assessed by the investigator.
5. Myocardial infarction within the last 6 months prior to or during Screening.
6. Criterion modified per Amendment 2

   6.1 Decompensated cardiac failure not receiving optimal medical treatment according to local guidelines.
7. Arrhythmias assessed as severe by the investigator.
8. Criterion modified per Amendment 2

   8.1 Criterion modified per Amendment 3

   8.2 Participants who either are planning to receive an implantable cardioverter defibrillator (ICD) or who already have one that has delivered shock therapy any time in the previous 1 year prior to Day 1. Participants with ICD are eligible if no shock therapy has been delivered in the previous 1 year prior to Day 1.
9. Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 90 days prior to or during Screening.
10. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH.
11. Overt features of pulmonary veno-occlusive disease (PVOD).
12. Significant emphysema as assessed by the investigator.
13. Criterion modified per Amendment 2

13.1 Known and documented severe hepatic impairment, eg, Child-Pugh Class C (see Section 10.13).[a]

14. Severe renal failure (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 or serum creatinine >2.5 mg/dL) based on central laboratory results from the Screening blood sample.

15. Criterion modified per Amendment 2

15.1 Treatment with prostacyclin, prostacyclin analogues or IP receptor agonists (ie, selexipag) within 90 days prior to randomization and/or prior to the RHC qualifying for enrollment, except those given at vasodilator testing during RHC.

16. Included on a lung transplant list or planned to be included until Visit 6 / Week 39.

17. Known or suspected uncontrolled thyroid disease as per investigator judgment.

18. Treatment with moderate inducers of CYP2C8, eg, rifampicin or strong inhibitors of CYP2C8, eg, gemfibrozil at or within 14 days prior to randomization.

19. Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to RHC qualifying for enrollment.

20. SBP <90 mmHg at Screening or at randomization.

21. Known allergies, hypersensitivity, or intolerance to selexipag or its excipients (refer to IB selexipag).

22. Planned or current treatment with another investigational intervention up to 90 days prior to randomization.

23. Criterion deleted per Amendment 3

24. Any condition for which, in the opinion of the investigator, participation would not be in the best interests of the participant (eg, compromise well-being), or that could prevent, limit, or confound the protocol-specified assessments.

25. Criterion modified per Amendment 3

25.1 Any acute or chronic impairment that may influence the ability to comply with study requirements such as to perform RHC, a reliable and reproducible 6MWT, or lung function tests.

[a] Note: The assessment of hepatic impairment (Child-Pugh Score) must be fully documented for patients who have clinical signs and evidence (from central and/or local lab) of hepatic impairment (see Section 10.13).

26. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

27. Pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 30 days after the last dose of study intervention.

NOTE: 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 randomization such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

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. Refer to Section 6.5, Concomitant Therapy 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).

5.4. Screen Failures

For participants who failed Screening, the following additional data will be recorded in the electronic Case Report Form (eCRF) if available: reason for Screening failure, baseline data collected until confirmation of the Screening failure.

Individuals who do not meet the criteria for participation in this study (Screening failure) may be rescreened once, if the reason for non-eligibility was transient (eg, abnormal laboratory test, insufficient wash-out period of a forbidden medication). All Screening assessments must be repeated at the time of rescreening. If the Screening RHC was done as per timing requirements indicated in Section 8.2.1.1.1, it does not need to be repeated. Rescreened participants will be assigned a different participant number than for the initial Screening.

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 and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

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

Selexipag and placebo will be manufactured and provided under the responsibility of the sponsor. Refer to the IB selexipag 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 in which the study sites are located. Labels must remain affixed to the bottles.

6.1.1. Description of Study Interventions

Selexipag 200 µg and matching placebo will be provided as identical yellow, round, non-debossed, film-coated tablets in childproof bottles containing 120 tablets.

6.1.2. Study Intervention Administration

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

Dosing frequency will be twice daily, except for participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s), for whom the dosing frequency is once daily.

In case of twice daily dosing, at the beginning of each up-titration step, the first dose is to be taken in the evening. In case of once daily dosing, participants must take the study intervention in the morning; hence the first dose of study intervention should be taken in the morning of Day 2.

Beginning with the morning of Visit 3, and at each visit thereafter up to the EOMOP visit, participants must take the morning study intervention dose before any visit-related procedure and preferably at the site. Tolerability may improve when study intervention is taken with food.

For the definition of study intervention overdose, refer to Section 6.8, Treatment of Overdose.

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.

6.1.3. Study Intervention Up-titration

Study intervention will be up-titrated to allow each participant to reach their iMTD, in the range of 200 µg to 1,600 µg (ie, 1 to 8 tablets) twice daily/once daily. Dosing frequency will be twice daily, except for participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s), who receive study intervention once daily.

Each participant will start with 1 tablet of study intervention, ie, selexipag (200 µg) or matching placebo, in the evening of Day 1 and will continue with 200 µg twice daily on Day 2. Participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s) will start with 200 µg once daily in the morning of Day 2.

The dose will be up-titrated by the investigator/delegate in 200 µg twice daily/once daily increments at weekly intervals during scheduled TCs until reaching the iMTD (see Table 1 and Figure 2).

If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment (refer to Section 6.5 for information on the allowed concomitant medication), the duration of the titration step can be prolonged to 2 weeks. If needed, the dose can be reduced by 200 µg twice daily/once daily.

The decision to not further up-titrate the dose will be based on the investigator's medical judgment based on the occurrence and severity of typical pharmacological effects of IP receptor agonists and the participant's individual tolerability (see also Section 2.3.4 and IB selexipag). At Week 12 (Visit 3), the twice daily/once daily dose reached for each participant is defined as the iMTD. This dose must be kept stable at least until Week 39 (Visit 6) but can be adjusted for safety and tolerability reasons.

Any study intervention interruption of 3 days or more will require a new up-titration to avoid tolerability-limiting side effects (see Section 7.1.1).

After Week 39, it is permitted to further up-titrate the dose for the participant, if necessary (up to the maximum of 1,600 µg twice daily/once daily, as applicable) in 200 µg twice daily/once daily increments at scheduled or unscheduled visits. Starting with Visit 3 and at all consecutive Visits up to and including the EOMOP Visit, 6MWT and RHC must be performed within 2 to 5 hours post-dose.

Table 1: Study Intervention Up-titration Scheme

Period	Dose regimen	Duration	
First dose	200 µg	On Day 1 in the evening (pm)	1 tablet
Up-titration	200 µg twice daily*,§	From Day 2 am to Day 8 am**	1 tablet twice daily§
	400 µg twice daily*,§	From Day 8 pm to Day 15 am**	2 tablets twice daily§
	600 µg twice daily*,§	From Day 15 pm to Day 22 am**	3 tablets twice daily§
	800 µg twice daily*,§	From Day 22 pm to Week 4 am**	4 tablets twice daily§
	1,000 µg twice daily*,§	From Week 4 pm to Week 5 am**	5 tablets twice daily§
	1,200 µg twice daily*,§	From Week 5 pm to Week 6 am**	6 tablets twice daily§

Period	Dose regimen	Duration	
	1,400 µg twice daily*,§ 1,600 µg twice daily*,§:	From Week 6 pm to Week 7 am** From Week 7 pm to Week 12 am**	7 tablets twice daily§ 8 tablets twice daily§
Maintenance	iMTD: 200 µg to 1,600 µg twice daily§	From Week 12 onwards	1–8 tablets twice daily§

am morning;; iMTD individual maximum tolerated dose; pm evening.
* Or the iMTD until Week 12.
** If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to 2 weeks.
§ For participants with moderate hepatic impairment (Child Pugh Class B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s) the dosing frequency is once daily. These participants must take the study intervention in the morning; hence the first dose of study intervention should be taken in the morning of Day 2.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Accountability

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 (number of dispensed bottles and date dispensed/number of tablets dispensed) to the participant, and the return of study intervention (date returned/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, he/she 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, used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention 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 participating 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by PH-specific therapy at baseline (yes vs no). The Interactive Web Response System (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

This study will be performed in a DB fashion.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical study team, or others as appropriate until after the time of the database lock (see Section 9.3) and unblinding.

Under normal circumstances, the investigator and study personnel, the participants, sponsor personnel directly involved in the conduct of the trial, and CRO personnel involved in the conduct of the study will remain blinded to the study intervention until after completion of the first analysis timepoint (see Section 9.3), or until the study is stopped prematurely. In order to preserve the blind of each individual participant until the primary analysis (see Section 4.1), the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the analyses for the

sponsor DMC. A statistical support group (SSG) independent from the study team will conduct the analyses and present unblinded results to the sponsor DMC (see Section 9).

The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the Investigator Site file and in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a participant in the study, unblinded SUSAR information will be provided to respective health authorities and Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) only. SUSARs will be reported to investigators in a blinded fashion. The intervention assignment will not be communicated to site personnel or to sponsor study team (see Section 8.4.3).

Participants who have had their intervention assignment unblinded may stay on study intervention after unblinding provided the following conditions are met: emergency unblinding for accidental or intentional overdose or medication error.

6.4. Study Intervention Compliance

Study intervention compliance is based on study intervention accountability (see Section 6.2). Study intervention compliance will be calculated by site personnel at each visit using the below formula and documented in the source data:

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

Between visits and overall study compliance are expected to be between 80% and 120%. 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.

6.5. Concomitant Therapy

Prestudy therapies administered up to 30 days before first dose of study intervention and any previous therapies for the treatment of PH (ERA, PDE5i, riociguat) and sarcoidosis (eg, infliximab, methotrexate, azathioprine, hydroxychloroquine, leflunomide, steroids) administered up to 90 days before the baseline RHC and 90 days before randomization, respectively, must be recorded in the eCRF at time of Screening.

Concomitant medications, except those listed below, are allowed during this study. Concomitant therapies must be recorded in the eCRF throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) or date of last contact (see Section 7.3).

All therapies (oxygen supplementation, prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the generic name, start/end dates of administration (as well as whether it was ongoing at start of intervention and/or EOS), route, dose, frequency and indication.

For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented in the AE section of the eCRF.

Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

The following medications and/or therapies are not allowed to be administered concomitantly with study intervention:

- Prostacyclin (epoprostenol), prostacyclin analogues (eg, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/UPTRAVI®) until study intervention discontinuation and if possible up to the post-baseline RHC at premature EOT before Week 26 (see Section 8.2.1.1.2).
- Strong inhibitors of CYP2C8 (eg, gemfibrozil) until study intervention discontinuation.
- Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to RHC at Week 26.
- Any other investigational drug up to 30 days after study intervention discontinuation.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Medications and/or therapies allowed to be administered concomitantly with study intervention, include, but are not limited to:

- Stable doses of PH-specific monotherapies (ie, riociguat, PDE5i, or ERA). Change in dose or initiation of new therapies for the treatment of PH are allowed as of Week 39 (Visit 6).
- Short-acting-beta-agonists (eg, salbutamol) and long-acting-beta-agonists, but must not be taken within 6 hours and 24 hours prior to spirometry testing, respectively.
- Single administration of prostacyclin or analogues used for acute vasodilator testing during an RHC procedure.
- Moderate inhibitors of CYP2C8. Dosing frequency of study intervention must be reduced to once daily if a moderate inhibitor of CYP2C8 (eg, clopidogrel, deferasirox, teriflunomide,

leflunomide) is concomitantly administered. Dosing frequency of selexipag should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped.

- Sarcoidosis-specific treatment, eg, infliximab, methotrexate, azathioprine, hydroxychloroquine, leflunomide, steroids. Initiation of new treatment or change in dose is allowed as of Week 39 (Visit 6).
- Strong inhibitors of UGT1A3 and UGT2B7 (eg, valproic acid, probenecid, and fluconazole). The effect of strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag and its active metabolite has not been studied. Caution is required when administering these medicinal products concomitantly with selexipag. A potential pharmacokinetic interaction with strong inhibitors of UGT1A3 and UGT2B7 cannot be excluded.

6.6. 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).

For participants who are unable to tolerate the protocol-specified dosing scheme, dose adjustments must follow the down-titration instructions (see Section 6.1).

6.7. Intervention After the End of the Study

After the participant has completed or discontinued the study, the investigator/delegate will explain to the participant what treatment(s)/medical care is necessary and available according to local regulations. If considered by the investigator to be in the best interests of the participant, the investigator can ask the sponsor to provide participants who completed the study and did not prematurely discontinue study intervention with selexipag. In this case, selexipag can be provided until access to commercial selexipag is possible in this indication in the participant's country of residence (according to local regulatory requirements), until selexipag can be accessed through another source in the country where he/she is living, or until the sponsor terminates clinical development of selexipag in this indication.

Investigators may re-contact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Section 10.3).

6.8. Treatment of Overdose

Overdose is defined by the intake of any single dose greater than 1,600 µg or a total daily dose greater than 3,200 µg (only in case subjects are on a twice daily regimen) (IB selexipag). 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.

Isolated cases of overdose up to 3,200 µg have been previously reported. Mild, transient nausea was the only reported consequence.

In the event of an 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, he/she believes that continued administration would be contrary to the best interests of the participant.

A participant's study intervention must be discontinued if:

- The investigator considers that for safety reasons or tolerability reasons (eg, AE) it is in the best interests of the participant to discontinue study intervention.
- The participant becomes pregnant. Refer to Section 10.5, Contraceptive Guidance and Collection of Pregnancy Information.
- If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If a subject has developed severe hepatic impairment (Child-Pugh Class C) at any time during the study, the study intervention must be permanently discontinued (see Section 10.13).
- Pulmonary edema due to PVOD occurs. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered. If confirmed, the study intervention must be discontinued.
- Study intervention interruptions exceeding 14 consecutive days.
- The participant withdraws consent to receive study intervention.

If a participant discontinues study intervention prematurely before the EOMOP visit, he/she will continue to perform the visits and assessments as scheduled until the EOMOP visit, provided the participant's consent for this limited participation in the study has not been withdrawn (see Section 7.2). The participant will be asked to return for the premature EOT visit within 7 days of

last intake of study intervention and for a safety follow-up TC 30 (+5) days after the last intake of study intervention. If the premature EOT visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated.

If a participant discontinues study intervention prematurely before the EOMOP visit and does not agree to continue to perform the visits and assessments as scheduled until the EOMOP visit, he/she will be asked to return for the premature EOT visit within 7 days of last intake of study intervention and for a safety follow-up TC 30 (+5) days after the last intake of study intervention, provided the participant's consent for this limited participation in the study has not been withdrawn. Long-term survival follow-up information will be collected yearly until death or the time of EOMOP (see Section 7.2 and Section 8.2.2.2).

If a participant discontinues study intervention prematurely after EOMOP but before the study results are available and the treatment assignment is unblinded, he/she will be asked to return for the premature EOT visit within 7 days of last intake of study intervention and for a safety follow-up TC 30 (+5) days after the last intake of study intervention, 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, then no additional assessments are allowed.

7.1.1. Temporary Discontinuation

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. Any study intervention interruption of 3 days or more will require a new up-titration starting with 1 tablet of study intervention (200 µg) twice daily/once daily. 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 participants' tolerability of the study drug prior to its interruption (see Section 6.1.2). Re-uptitration to a previously reached dose can be done at scheduled or unscheduled TCs or visits, respectively.

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 in the eCRF.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will not be automatically withdrawn from the study if they have to discontinue study intervention before EOT (see Section 7.1).

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

- Lost to follow-up.
- Withdrawal of consent.

- Death.
- Participant is poorly compliant with study procedures, visits, and assessments, preferably after evaluation and discussion between the investigator and the sponsor.
- The investigator considers 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 completing the study (see Section 4.4.2) for any reason (except for death or withdrawal of consent), every attempt should be made to schedule a last appointment/TC to assess the safety and well-being of the participant, collect unused study intervention and discuss follow-up medical care. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed. 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.

A participant who prematurely discontinues study intervention before the EOMOP visit and declines 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, continuing with survival follow-up, consulting with family members, contacting the participant's other physicians, medical records, database searches, and use of locator agencies at study completion), as local regulations permit.

Refer to Section 7.3 for more information on the required procedure to follow if a participant is lost to follow-up.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document.

Study intervention assigned to the withdrawn participant may not be assigned to another participant.

If participants prematurely discontinue study intervention or withdraw consent, participants will not be replaced.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample

destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up attempts should be made, prior to randomization 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 he or she 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 TCs, 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, they will be considered lost to follow-up, and hence will be withdrawn from the study (see Section 7.2).

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, safety, and biomarker measurements applicable to this study. For all visits, the participants must be seen or called on the designated day with an allowed visit window per the Schedule of Activities. 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.

The following order of assessments is recommended, as applicable:

1) PROs completed at each site Visit: SF-12, King's SQ, PGA-S
2) Investigator to complete CGI-S and CGI-C
3) Safety assessments (see Section 8.3 for the order of safety assessments)
4) Pulmonary function tests
5) WHO FC
6) 6MWT* and oxygen saturation and Borg CR Scale® (CR10) (pre- and post-6MWT)
7) Blood samples for hematology, and clinical chemistry tests, NT-proBNP, and/or biomarkers
8) Arterial Blood Gas analysis (if possible, during RHC)
9) RHC*

*Assessments to be performed within 2 to 5 hours post-dose.

Actual dates and times of assessments (where applicable) will be recorded in the eCRF.

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

The maximum total blood volume to be collected during the entire study from each participant will vary depending on when the patient enters the study. The total blood volume (excluding the serum β-hCG pregnancy test and arterial blood gas) to be collected at each visit from screening to Week 39/Visit 6 and from Week 65/Visit 7 until EOT will be approximately 21.5 mL and 9.5 mL, respectively (see Table 2). An additional 1 mL to 3 mL of blood may be collected during RHC to measure CO according to Fick's method.

Table 2: Volume of Blood to be Collected From Each Participant per Visit

Type of Sample	Volume per Sample (mL)	Volume per sample (mL) at each Visit until Visit 6[e]	Volume per sample (mL) at each Visit from Visit 7 to EOT[e]
Safety (including Screening and post-intervention assessments)			
- Hematology	2	2	2
- Serum chemistry[b]	7.5	7.5	7.5
- NT-proBNP[g]	2.5	2.5	0
- Serum β-hCG pregnancy tests[d]	2.5	2.5	2.5
Exploratory biomarker plasma sample[c,h]	4.5	4.5	0
Exploratory biomarker serum sample[c,h]	5	5	0
Arterial Blood Gas[f]	2	2	0
Approximate Total per Visit[a]		21.5	9.5

β hCG β human chorionic gonadotropin; EOT = end-of-treatment; NT proBNP N terminal pro b type natriuretic peptide.

a. The approximate total per visit does not include the required volume for the serum β-hCG pregnancy test and the arterial blood gas.
b. See Section 10.2 for more information.
c. Optional sample (see Section 8.5).
d. Only for women at screening or in case of a positive urine pregnancy test, as no serum β-hCG pregnancy test will be performed in male participants.
e. Repeated or unscheduled samples may be taken for safety reasons or technical issues with the samples.
f. Arterial blood gas only at screening, and Week 26.
g. Not collected at Screening.
h. Not collected at Screening and Week 20.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Unscheduled Visits

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

An unscheduled visit including all mandatory assessments described in the Schedule of Activities must be performed in case of the following occurring outside of a scheduled visit:

- Any new AE suggestive of RHF or SAPH disease progression.
- Any new evidence of a decrease in exercise capacity or increase in dyspnea.
- Any change in dose/initiation of new PH-specific therapies and/or up-titration of study intervention beyond the planned titration phase.

The date of the visit and the reason for the visit, as well as data related to study-specific assessments performed at unscheduled visits, will be recorded in the eCRF.

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.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, shipment of samples, and reporting of results are found in the laboratory manual that will be provided. 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:

- Investigator's Brochure
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual, requisition forms, and sampling supplies
- IWRS Manual
- PRO questionnaires, CRO questionnaires, completion guidelines, and electronic devices
- Actigraphy devices and user guidelines
- eCRF completion guidelines
- SAE form and completion guideline
- Pregnancy forms
- Product quality complaint (PQC) form
- Study participant cards
- Pregnancy cards
- RHC guidance document
- 6MWT guidance document

8.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic data to be collected on all randomized participants include: age, sex, race and ethnicity (where local regulations permit), weight and height, date of the initial SAPH diagnosis, WHO FC, and smoking status (never, former, current).

All relevant medical history / current medical conditions based on the investigator's judgment (eg, chronic and ongoing acute conditions, serious past conditions) present 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.

For participants who are naïve to PH-specific therapies, the reason(s) for not prescribing ERA/PDE-5 inhibitors/riociguat are collected in the eCRF (not available, not reimbursed, contraindicated, not tolerated, other).

8.2. Efficacy Assessments

Data obtained from the efficacy assessments listed below will be recorded in the eCRF, unless stated otherwise.

8.2.1. Primary Efficacy Endpoint Assessment

8.2.1.1. Right Heart Catheterization

Guidance for the RHC assessment is provided in the SPHINX RHC guidance document. The following hemodynamic variables are to be collected: heart rate, peripheral systolic and diastolic blood pressure (SBP and DBP, respectively), pulmonary artery wedge pressure (PAWP; alternatively, LVEDP), mRAP, systolic/diastolic pulmonary artery pressures (sPAP/dPAP), CO, and SvO_2.

8.2.1.1.1. Baseline RHC

All participants must have a baseline RHC.

A historical RHC is allowed, if following criteria are met:

- All required variables as per SPHINX RHC guidance document are available.
- It is feasible to perform the Week 26 RHC as described in Section 8.2.1.1.2
- Historical RHC was performed:

  Within 90 days prior to randomization,

  At least 90 days after last change in PH-specific therapies (ie, change in dose or initiation of new class of drugs).

  At least 90 days after starting a new specific anti-inflammatory treatment for sarcoidosis.

  At least 30 days after last change in dose of specific anti-inflammatory treatment for sarcoidosis.

If no historical results meeting the above criteria are available, an RHC, according to the SPHINX RHC guidance document must be performed during the Screening period only if all other inclusion criteria are met and none of the exclusion criteria is met.

8.2.1.1.2. Week 26 RHC

At Week 26 an RHC will be performed within 2 to 5 hours post-dose. It is recommended that any post-baseline RHC is performed by the same operator, according to the same standards and procedures and in the same catheterization laboratory. Guidance for the RHC assessment is provided in the SPHINX RHC guidance document.

If a participant prematurely discontinues study intervention between Week 12 and Week 26, it is recommended to perform an RHC within 3 days after last study intervention dose.

An RHC performed at any unscheduled visit must be entered into the eCRF.

8.2.2. Exploratory Endpoint Assessments

8.2.2.1. Clinical Worsening and Hospitalization Related to PH-worsening

The following data (obtained as part of other assessments) are required to derive TTCW (see Section 3): reporting of death, hospitalization, WHO FC, concomitant medications, AEs and SAEs. The following cases will be adjudicated by the CEC: hospitalization, increase (ie, worsening) in WHO FC and initiation of new PH-therapies. For all participants, assessment and reporting of any further disease progression will continue up to the EOMOP visit (see Section 4.1).

8.2.2.2. Survival Follow-up

For participants who prematurely discontinue study intervention and do not agree to continue to perform the visits and assessments up to EOMOP, long-term survival information will be collected yearly until death or the time of EOMOP (see Sections 7.1, 7.2, and 4.1). The following information will be collected in the eCRF: vital status (including date and cause of death).

8.2.2.3. Exercise Capacity

8.2.2.3.1. 6MWT

Exercise capacity will be measured by the 6MWT (ATS Guidelines 2002; Holland 2014). The 6MWT is a non-encouraged test that measures the distance walked in 6 minutes (6MWD). Guidelines on execution of the 6MWT will be provided in the separate SPHINX 6MWT guidance document.

During the entire study, the 6MWT must be performed within 2 to 5 hours post-dose and prior to the RHC (if applicable). The time of the study intervention morning dose intake will be recorded in the eCRF. For participants who have never performed a 6MWT previously, a training test will be requested before the Screening 6MWT for inclusion (data from the training test are not collected in eCRF).

If a 6MWT cannot be performed at a scheduled visit beyond Visit 2 or at an unscheduled visit, a reason must be provided (ie, PH-related or other).

8.2.2.3.2. Daily Life Physical Activity (DLPA) and Sleep Parameters

DLPA and sleep parameters are assessed via an actigraphy device. The device is given to the participant at Visit 1 (Screening Visit), and the participant is instructed to wear the actigraphy device on the wrist for 2 weeks during the screening period and following site visits. Detailed instructions for use of the actigraphy device and accessories are provided to participants via a participant guide.

The actigraphy device does not display collected data, ie, the participants do not have access to their activity measurements, as this could influence their behavior. Data will be uploaded to the vendor as described in the participant guide.

The data received will be monitored for compliance. Should corrective actions be necessary, participants may be contacted from the site staff.

The data from the actigraphy device will be collected by the vendor, who will send the results to the sponsor, but the results will not be recorded in the eCRF.

8.2.2.4. Oxygen Saturation (Pre- and Post-6MWT)

Oxygen saturation will be measured using pulse oximetry (performed as per standard practice at the study site) just before starting and immediately after stopping the 6MWT.

8.2.2.5. Dyspnea (Pre- and Post-6MWT)

Dyspnea will be assessed by the Borg CR Scale® (CR10) (Borg 1970, 1998), a scale used to quantify the degree of shortness of breath as per the SPHINX 6MWT guidance. Dyspnea will be evaluated by each individual participant immediately before starting and after stopping the 6MWT.

8.2.2.6. WHO FC

WHO FC, as defined in Section 10.6, will be assessed.

8.2.2.7. NT-proBNP

A blood sample for the analysis of NT-proBNP will be drawn (see Section 10.2). Details about the collection, sampling, storage, shipment procedures and reporting of results and abnormal findings can be found in the central laboratory manual.

8.2.2.8. Patient-reported Outcomes

The following PRO instruments will not be administered to illiterate participants and will not be administered to a participant when the instrument is not available in a language that can be easily understood and read by the participant. It is recommended that the PROs are completed prior to any clinical assessments.

The PROs are completed on an electronic device. As participants need to complete the PAH-SYMPACT™ at home, participants can take home the electronic device after being trained by the site staff during Visit 1. Participants must return the mobile device to the site at Visit 7. Data will be transferred daily to an electronic database immediately upon completion of the questionnaire via a cellular connection to the vendor. The data received will be checked for completion compliance. The site will be informed if the questionnaire has not been completed as per protocol. Should corrective actions be necessary, participants may be contacted either from the site staff or via messages onto the mobile device from the vendor. All other PROs will be completed on an electronic device at the site.

The data from the mobile device will be collected by the vendor, who will send the results to the sponsor, but are not recorded in the eCRF.

8.2.2.8.1. PAH-SYMPACT™ questionnaire

The PAH-SYMPACT™ (Section 10.7) (Chin 2018) questionnaire is a PRO instrument that was developed by Actelion Pharmaceuticals Ltd. (McCollister 2016). This questionnaire has been developed and validated for use in PAH patients. Content validity of the questionnaire is being tested with SAPH patients in a separate stand-alone qualitative interview study.

The PAH-SYMPACT™ consists of 2 parts:

- The symptom part is completed for the 7 consecutive days following the visit at site (ie, starting the day following the visit day).
- The impact part is completed once, on the seventh day of the symptoms diary data collection period, together with the symptom part (ie, in the evening).

The PAH-SYMPACT™ should be completed in the evening before bedtime.

8.2.2.8.2. SF-12

The SF-12v2® Healthy Survey (Section 10.8) (Gandek 1998) is a quality of life self-assessment derived from the SF-36v2® (Health Survey© 1996, 2000 by Medical Outcomes Trust and Quality Metric Incorporated). It has 12 items measuring 8 scales, including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health (Gandek 1998). The SF-12 is scored using norm-based scoring in the same way as for the SF-36v2®.

8.2.2.8.3. King's Sarcoidosis Questionnaire (KSQ)

The KSQ (Section 10.9) is a health status questionnaire developed and validated for patients with sarcoidosis. It is brief, adaptable to individual patients and assesses general and organ-specific health status. The KSQ consists of 5 modules: General health status (10 items), Lung (6 items), Skin (3 items), Eye (7 items), Medications (3 items). The organ-specific modules can be combined with the General health status module to assess overall health status for patients depending on which organs are affected by their disease (Patel 2013). The KSQ is summarized as a number between 1 and 100, with higher numbers indicating better health.

8.2.2.8.4. Patient Global Assessment of Disease Severity (PGA-S)

The PGA-S (Section 10.10) is a 6-point single item self-evaluation scale (Nikiphorou 2016; Scott 1977). Participants will be asked to rate the overall severity of their disease on the day of administration, with responses of none, very mild, mild, moderate, severe or very severe.

8.2.2.9. Clinician-reported Outcomes (CROs)

The CROs (CGI-S and CGI-C) (Busner 2007; Guy 1976) are completed on an electronic device. The data from the mobile device will be collected by the vendor, who will send the results to the sponsor. The results are not recorded in the eCRF.

8.2.2.9.1. Clinician Global Impression of Severity (CGI-S)

The CGI-S (Section 10.11) is a 6-point single-item scale. The investigator/delegate will rate the overall severity of the participant's disease on the day of administration with responses of none, very mild, mild, moderate, severe or very severe.

8.2.2.9.2. Clinician Global Impression of Change (CGI-C)

The CGI-C (Section 10.12) is a 7-point single-item scale. The investigator/delegate will rate the overall participant's change of the participant's disease since baseline with responses of very much better, moderately better, a little better, no change, a little worse, moderately worse or very much worse.

8.3. Safety Assessments

Safety and tolerability will be evaluated throughout this study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) or date of last contact (see Section 7.3).

The standard safety assessments to evaluate the safety and tolerability of selexipag in this study include reporting and follow-up of (S)AEs, pregnancies, vital signs, physical examination, ECG, and safety laboratory tests. In addition, pulmonary function, DL_{CO} and arterial blood gas will be monitored.

Details regarding the sponsor DMC and SC are provided in Committees Structure in Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.4 and Section 10.4.

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

Any clinically significant abnormalities persisting at the end of the study/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 7.3).

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Schedule of Activities.

8.3.1. Physical Examination

Physical examination includes the examination of the general appearance, heart, lungs, extremities, eyes. Other exams will be performed if indicated, based on medical history and/or symptoms.

Height will be measured without shoes.

Body weight will be measured in indoor clothing but without shoes.

Clinically relevant findings (other than those related to SAPH) that are present prior to signing of ICF must be recorded on the Medical History eCRF page. Physical examination findings made after signing of ICF, which meet the definition of an AE must be recorded on the AE page of the eCRF.

8.3.2. Vital Signs

Pulse rate, SBP and DBP will be assessed in a supine or sitting position. 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.

Vital signs data will be recorded in the eCRF.

8.3.3. Electrocardiogram

A single standard 12-lead ECG will be performed and interpreted locally.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement are scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Clinically relevant ECG findings that are present prior to the initiation of study intervention must be documented in the Medical History section of the eCRF. Clinically relevant ECG findings found after the study intervention initiation that were not present at Screening or that worsened during the study, meet the definition of an AE and should be recorded on the Adverse Event form of the eCRF.

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.2. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

The laboratory reports from the central laboratory must be filed with the source documents. The local laboratory results (with the corresponding normal ranges), if applicable per Section 10.2, must be recorded in the eCRF.

Details about the collection, sampling, storage, shipment procedures and reporting of results and abnormal findings can be found in the central laboratory manual.

8.3.5. Pulmonary Function Tests

The pulmonary function tests (spirometry and DL_{CO}) must be performed by experienced staff, such as a pulmonary function technician or expert.

8.3.5.1. Spirometry

Spirometry tests will be conducted according to the ATS/ERS (Graham 2019; Miller 2005a,b).

It is recommended that all spirometry assessments are performed at the same time and under same conditions throughout the study. Participants must refrain from taking short-acting-beta-agonists (eg, salbutamol) for 6 hours and long-acting-beta-agonists for 24 hours prior to spirometry testing (see Section 6.5). If taken, the test should be rescheduled. To perform the spirometry test, participants will be rested for a minimum of 5 minutes prior to start.

The following variables will be collected at Screening (Visit 1) and subsequent Visits where applicable: FEV_1 and FVC.

8.3.5.2. Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO})

The diffusing capacity of the lungs, measured using carbon monoxide (DL_{CO}) will be conducted according to the ATS/ERS guidelines and will be assessed by the single-breath method (Graham 2017). DL_{CO} efforts, up to a maximum of 5, will be performed to produce at least 2 technically acceptable and repeatable traces (according to ATS/ERS guideline criteria). There must be a minimal interval of at least 4 minutes between each effort performed.

8.3.6. Resting Arterial Blood Gas

Measurement of resting ABG will be performed as per site standard. It is recommended to be performed during RHC if possible. The Week 26 ABG assessment should be performed under the same conditions, eg, same oxygen rate (if applicable), as the ABG performed at screening. If a historical RHC, meeting the criteria in Section 8.2.1.1.1, is available and if ABG was part of that RHC, it is not necessary to repeat ABG during screening, and the available results can be entered into the eCRF. Values to be recorded in the eCRF include $PaCO_2$, PaO_2, SaO_2, fraction of inspired oxygen (FiO_2) and barometric pressure on the day of the assessment.

8.4. 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) or date of last contact (see Section 7.3).

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

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported on specific AE pages of the eCRF throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4.1) 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 visit, must be reported on AE pages of the eCRF and on the SAE 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 SAE Form and Safety Report Form of the CRF, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

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.

8.4.2. 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: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.3. 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 SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the

IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary unless otherwise specified.

8.4.4. Pregnancy

All initial reports of pregnancy in female participants or female 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 the SAE reporting form. Any female participant who becomes pregnant during the study must discontinue further study intervention (see Section 7.1).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant 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.

8.5. Biomarkers

Biomarker analysis is optional for each participant. A biomarker-specific ICF should be signed prior to collection of any samples for biomarker analysis.

Plasma and serum samples for the analysis of pharmacodynamic and disease-related biomarkers (see Section 4.2) can be collected at timepoints indicated in the Schedule of Activities and archived for future analysis from all participants. Refer to the laboratory manual for detailed instructions for sample collection, processing and shipment of archive samples for exploratory research.

The biomarkers included in the analysis will be specified in a biomarker plan.

Refer to Section 10.3 for more information on the long-term retention of samples collected for biomarker analysis.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or delegated to a Contract Research Organization under the responsibility of the sponsor. Unblinded analyses for the sponsor DMC will be performed by an SSG independent from the study team to protect from unblinding. 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).

Data collected during the study will be summarized by intervention group and, where appropriate and applicable, compared between intervention groups with hypothesis test.

Individual listings for participant demographics, baseline characteristics, and endpoint-related data will be provided as applicable and will be detailed in the SAP.

9.1. Populations for Analyses

For analysis purposes, the following populations are defined:

Table 3: Overview of the Different Populations for Analyses.

Population	Description
Screened Analysis Set (SCR)	All participants who were screened and received a participant identification number.
Randomized Set (RS)	All participants assigned to a study intervention.
Full Analysis Set (FAS)	All patients from the RS who took at least one dose of study intervention and for whom the baseline pulmonary vascular resistance is non-missing.
Per-Protocol Analysis Set (PPS)	All participants from the FAS who received the assigned study intervention and who complied with the protocol sufficiently to be likely to exhibit the intervention effects.
Safety Analysis Set (SAS)	All participants who received at least one dose of study intervention. Participants will be analyzed according to the intervention they actually received.

PVR and all other efficacy analyses will primarily be evaluated on the Full Analysis Set (FAS). The PVR analyses will also be performed on the Per-Protocol Analysis Set (PPS), unless the number of subjects in the PPS and the FAS differ by less than 5%, in which case, no analyses will be performed using the PPS. Safety endpoints will be primarily evaluated on the SAS.

9.2. Statistical Hypotheses

The null and alternative hypotheses are described in Section 9.5.1.1 together with the estimand and statistical model definitions.

9.3. Analysis Timepoints

There are two analysis timepoints as defined in Section 4.1.

Details on the statistical analyses performed at each of the different Analysis Timepoints will be specified in the SAP.

9.4. Sample Size

The calculation of sample size was approximated by Z-test for superiority on the log-transformed PVR post- to pre- percent of baseline as defined in Section 9.5.1.1) using the software package EAST™ version 6.4.0.1 for the difference of two means.

In order to guarantee the appropriate design characteristics (see assumptions in Section 9.4.1), a total of 74 patients is required (ie, 37 patients per treatment arm).

9.4.1. Sample Size Assumptions

In a clinical study with bosentan in participants with SAPH (BOSAPAH-1), the observed GM ratio for *PVR post to pre percent* (defined in Section 9.5.1.1) was around 0.7 in 35 participants with SAPH at Week 16 (bosentan vs placebo) (Baughman 2014). It was also 0.7 in the NS-304/-02 study in 35 participants with PAH at Week 17 (selexipag vs placebo, with CV of *PVR post to pre percent* 0.28 vs 0.08). In the CTEPH studies MERIT-1 (80 participants) and BENEFIT (157 participants) the observed CVs of *PVR post to pre percent* approached 0.4. The blinded interim estimate in 79 participants of the TRITON study gives a CV of 0.5.

Sample size is calculated based on the statistical requirements to detect a clinically relevant difference between the selexipag and placebo groups using a 1:1 randomization ratio, a two-sided Type I error of 5% and a Type II error of 10% (90% power).

The following assumptions were made:

- A ratio of the GM of Week 26 (or premature EOT) to Baseline PVR values equal to 0.70 ie, a 30% relative decrease (improvement) in GM as compared to placebo;
- A coefficient of variation (CV) of the ratio of 0.50;
- Normal distribution for the $\log_e$-transformed ratio of Week 26 (or premature EOT) to baseline PVR values.

Based on the above assumptions, 74 subjects are required to establish the superiority of selexipag vs placebo with 90% power to correctly reject a false null hypothesis in favor of the alternative hypothesis.

9.4.2. Sample Size Sensitivity

With a fixed sample size of 74, the power for showing superiority of selexipag over placebo depends on the ratio of geometric means (GMs) and the CV of the percent of baseline PVR at Week 26 (or premature EOT). Table 4 displays power calculations for different assumptions for these two parameters and a two-sided α 0.05.

Table 4: Sample size sensitivity for the main analysis

Scenario	Ratio of GMs	CV	Power
Sensitivity 1	0.65	0.45	99%
Sensitivity 2	0.65	0.50	97%
Sensitivity 3	0.70	0.45	94%
Original	**0.70**	**0.50**	**90%**
Sensitivity 4	0.75	0.45	82%
Sensitivity 5	0.75	0.50	74%

CV = coefficient of variation; GM geometric mean.

Figures in **bold red** correspond to the sample size calculation in the paragraph above.

9.5. Statistical Analyses

9.5.1. Efficacy Analyses

9.5.1.1. Primary Efficacy Analysis

Definition of PVR Endpoint

The primary endpoint is PVR on study intervention at peak concentration up to Week 26, ie, at Week 26 or at premature EOT in case of discontinuation of study intervention before Week 26.

Estimand

The primary PVR estimand is described according to the following four attributes:

A. Population: FAS (Full analysis set), as randomized.

B. Variable: Per each patient, the absolute change from baseline to Week 26 (or premature EOT) visit of the natural log-transformed PVR values will be estimated.

The corresponding ratio of the PVR value post-intervention initiation at Week 26 (or premature EOT) (post) vs the PVR value pre-intervention initiation at baseline (pre), expressed as a percentage will also be estimated, ie:

$$PVR\ post\ to\ pre\ percent = \left(\frac{PVR\ at\ Week\ 26\ (or\ premature\ EOT)}{PVR\ at\ baseline}\right) \times 100\ (\%)$$

C. Intercurrent events (events that preclude observation of the variable or affect its interpretation):

- Death occurring prior to Week 26 (or premature EOT) visit,
- Initiation of prostacyclin (epoprostenol), prostacyclin-analogs (eg, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/UPTRAVI) for any reason prior to post-baseline RHC,
- Study intervention discontinuation/interruption for more than 3 days immediately prior to the post-baseline RHC

D. Population-level summary: Ratio of the GM of the *PVR post to pre percent* between selexipag and placebo, obtained by exponentiation of the difference in means of the natural logarithm transformed *PVR post to pre percent* between selexipag and placebo:

$$\frac{GM(PVR\ post\ to\ pre\ percent\ in\ selexipag)}{GM(PVR\ post\ to\ pre\ percent\ in\ placebo)}$$

This estimand targets the effect of treatment initiation on the variable measurement prior to the occurrence of death or introduction of prohibited PH-specific medication and follows a "while on

treatment" strategy. For the purpose of the primary endpoint, on-treatment is defined as up to 3 days after last study intervention intake.

Intercurrent events will be handled as follows:

- "Death occurring prior to the post-baseline RHC" will be addressed by imputing the post-baseline PVR value using the missing data rules specified in subsequent sections.
- Initiation of prostacyclin (epoprostenol), prostacyclin analogs (eg, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/UPTRAVI) for any reason prior to post-baseline RHC" will be addressed by disregarding the post-baseline PVR assessments and imputing them using the missing data rules specified in subsequent sections.
- "Study intervention discontinuation/interruption for more than 3 days immediately prior to the post-baseline RHC" will be addressed by disregarding the PVR assessments obtained more than 3 days after study intervention discontinuation and imputing them using the missing data rules specified in subsequent sections.

Hypotheses

The hypotheses for the primary endpoint of PVR at peak concentration at Week 26 (or premature EOT) are formulated in terms of GM of *PVR post to pre percent* (as defined above) in participants treated with selexipag ($GM_{selexipag}$) versus placebo ($GM_{placebo}$):

H_0: $GM_{selexipag} / GM_{placebo}$ 1

H_A: $GM_{selexipag} / GM_{placebo} \neq 1$

Statistical Model

The null hypothesis is planned to be tested in the FAS by means of an ANCOVA model on the natural logarithm transformed *PVR post to pre percent*. Model covariates will include randomized intervention, stratification factor and the natural logarithm transformed baseline PVR value. The results will be presented on the original scale (GM) after exponentiation of the absolute adjusted mean changes obtained on the natural log scale:

Handling of Missing Data

By design, only one post-baseline PVR measurement will be taken at the time of the scheduled Week 26 or at the premature EOT visit. In some instances, the Week 26 (or premature EOT) assessment may be missing with no other post-baseline assessment available.

Imputation methods for PVR will be specific to the reason for missing data.

The baseline reference value for PVR is based on the last RHC performed prior to study intervention initiation.

If PVR cannot be calculated due to missing PAWP, the following conventions will be applied for the calculation at a visit at which both mPAP and CO are assessed and not missing:

1. If only PAWP is missing, then the LVEDP will be used.
2. If PAWP and LVEDP are missing both at baseline and post-baseline, the missing PAWP is imputed using the median of all values observed at the respective time point in all subjects from the same randomized intervention group.
3. If PAWP and LVEDP are missing either at baseline or at post-baseline, the available PAWP for the subject is used as a substitute for the missing PAWP.

If a post-baseline PVR assessment is missing up to Week 26, the following missing data imputation rules will be used:

- If a participant dies without a post-baseline value, then the missing *PVR post to pre fold* value is imputed with the largest *PVR post to pre percent* value for post-baseline amongst all participants in the same analysis set. The resulting imputed post-baseline PVR is the product of this imputed *PVR post to pre percent* value and the respective baseline PVR value.
- If a participant experiences clinical worsening, with a subsequent missing *PVR post to pre fold* value, the post-baseline value is imputed with the 75th percentile of the *PVR post to pre fold* values from all participants in the same analysis set. The resulting imputed post-baseline PVR is the product of this imputed *PVR post to pre fold* value and the respective baseline PVR value.
- If the participant is alive and does not experience clinical worsening, then the missing *PVR post to pre fold* value is imputed with the 50th percentile of the *PVR post to pre fold* values from all participants in the same intervention group and analysis set. The resulting imputed post-baseline PVR is the product of this imputed *PVR post to pre fold* value and the respective baseline PVR value.

Main Analysis

The analyses of the primary efficacy endpoint will be tested in the FAS using the ANCOVA model.

From the ANCOVA model, *PVR post to pre percent* will be summarized by intervention group using covariate adjusted- GM and corresponding 2-sided 95% CI. The between-group ratio of GM with corresponding 95% 2-sided CI and p-value will be displayed as the -placebo corrected intervention effect.

For each intervention group, the least square mean and 2-sided 95% CI of the natural logarithm of the *PVR post to pre percent* will be inversely transformed using the exponential function and multiplied by 100 to provide the GM of the *PVR post to pre percent* and the corresponding 2-sided 95% CI, expressed as a percentage.

Absolute values at baseline and post-baseline as well as absolute pre-post changes from baseline to post-baseline for PVR will be summarized using descriptive statistics.

Supportive/Sensitivity Analyses

Sensitivity analyses will be conducted using alternative imputation rules to assess the imputation assumptions of the main statistical analysis for PVR at Week 26 (or premature EOT).

Furthermore, a sensitivity analysis of PVR at Week 26 (or premature EOT) will be conducted in the per-protocol analysis set to assess the robustness of the results of the main statistical analysis against protocol deviations leading to exclusion from the PPS.

Details of the sensitivity analyses and other imputation approaches will be specified in the SAP.

9.5.1.2. Secondary Efficacy Analyses

There are no secondary endpoints for which confirmatory hypotheses are tested with adequate control of type I error. All efficacy endpoints other than PVR are exploratory; a general statistical analysis strategy is briefly discussed in Section 9.5.1.3. The full details will be provided in the SAP.

9.5.1.3. Other Efficacy Analyses

For continuous and categorical endpoints, where applicable, the response profiles over time (eg, change from baseline, proportions of participants by categorical endpoint categories) will be inspected graphically and by the usual summary statistics at each visit (with 95% CIs) up to the EOMOP visit by randomized treatment group on the RS. Two sets of profiles will be provided: one considering assessments measured on study intervention up to the EOMOP visit, and one including all data collected up to the EOMOP visit regardless of treatment discontinuations.

Time-to-event endpoints will be analyzed using the Kaplan-Meier method by randomized treatment group up to EOMOP, regardless of study intervention discontinuations.

9.5.2. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Intervention-emergent adverse events are AEs with onset during the intervention period or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Summaries will be by intervention (selexipag or placebo) and will include all events collected throughout the study.

The AEs of special interest will be defined in the SAP.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint by intervention group. Frequency tabulations of the abnormalities will be made.

Vital Signs

Descriptive statistics of pulse rate, SBP and DBP values and changes from baseline will be summarized at each scheduled timepoint by intervention group.

Supplemental Oxygen Rate

Descriptive statistics of values and changes from baseline in supplemental oxygen rate will be summarized by intervention group.

Pulmonary Function Tests

Descriptive statistics of values and changes from baseline in D_{LCO} and FVC will be summarized by intervention group.

Arterial Blood Gas

Descriptive statistics of values and changes from baseline in ABG parameters will be summarized by intervention group.

9.5.2.1. Study Safety Monitoring

Study safety information (AEs, SAEs, laboratory values, PFTs, D_{LCO} and vital signs) is monitored and reviewed on a continuous basis by the sponsor's clinical study team (to ensure participant's safety as well as data quality). In addition, a sponsor DMC monitors safety data (see Section 9.6). 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.

9.5.3. Biomarkers Analyses

Biomarker samples will be used to generate plasma and serum marker data for computational analyses (see Section 8.5). These analyses are considered exploratory and the results will be reported separately from this study.

Changes in plasma and serum biomarkers over time will be summarized by intervention group. Associations between baseline levels and changes from baseline in selected markers and clinical responses will be explored.

9.6. Data Monitoring Committee

A sponsor DMC will be established as noted in Committees Structure in Section 10.3.

The sponsor DMC has overall responsibility for safeguarding the interests of participants by monitoring safety data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring the study is conducted with the highest scientific and ethical standards.

Detailed information on the sponsor DMC is available in Section 10.3.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
ASO	arteriosclerosis obliterans
ATS	American Thoracic Society
BP	blood pressure
CGI-C	Clinician Global impression of Change
CGI-S	Clinician Global impression of Severity
CHD	coronary heart disease
CI	confidence interval
CIn	cardiac index
CRO	clinician-reported outcome
CO	cardiac output
CRF	case report form(s) (paper or electronic as appropriate for this study)
CTEPH	chronic thromboembolic pulmonary hypertension
CV	coefficient of variation
CYP	cytochrome P450
DB	double-blind
DBP	diastolic blood pressure
DL_{CO}	diffusing capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
dPAP	diastolic pulmonary artery pressure
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
EOMOP	end-of-main-observation-period
EOS	end-of-study
ERA	endothelin receptor antagonist
FAS	Full Analysis Set
FC	functional class
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GM	geometric mean
HRT	hormonal replacement therapy
IC	intermittent claudication
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
iMTD	individual maximum tolerated dose
IP	prostacyclin
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	Interactive Web Response System
KSQ	King's sarcoidosis questionnaire
LHF	left heart failure
LSS	lumbar spinal stenosis

LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary arterial pressure
mRAP	mean right atrial pressure
NT-proBNP	N--terminal pro b-type natriuretic peptide
O	Optional
PAH	pulmonary arterial hypertension
PAH-SYMPACT™	Pulmonary Arterial Hypertension-Symptoms and Impact
PAP	pulmonary artery pressure
PAWP	pulmonary artery wedge pressure
PDE5i	phosphodiesterase type-5 inhibitor
PGA-S	Patient Global Assessment of Severity
PH	pulmonary hypertension
PPS	Per-Protocol Analysis Set
PQC	product quality complaint
PRO	patient-reported outcome
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
QoL	quality of life
RBC	red blood cell
RHC	right heart catheterization
RHF	right heart failure
RS	randomized set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAPH	sarcoidosis-associated PH
SAS	Safety Analysis Set
SBP	systolic blood pressure
SC	Steering Committee
SCR	Screened Analysis Set
SF-12	12-Item Short Form Health Survey
sPAP	systolic pulmonary artery pressure
SpO_2	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
SvO_2	venous oxygen saturation
T3	free tri-iodothyronine
T4	free thyroxin
TC	telephone call
TSH	thyroid stimulating hormone
TTCW	time to clinical worsening
WHO	World Health Organization
WOCBP	women of childbearing potential
β-hCG	β-human chorionic gonadotropin

10.2. Appendix 2: Clinical Laboratory Tests

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

If the results from the central laboratory are not available in time for randomization of the participant, an additional blood sample may be drawn to verify eligibility based on a local laboratory test. The local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF.

Other exceptional circumstances that require recording of local laboratory results (with corresponding normal ranges) include hospitalization of the participant due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If central laboratory samples are lost or cannot be analyzed for any reason, the investigator will consider collecting an additional sample as soon as possible for repeat analysis, if deemed medically necessary.

Central laboratory reports will be sent to the investigator.

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 8.4 and Section 10.4).

The participants do not need to be fasted prior to the laboratory tests.

Details about the collection, sampling, storage, shipment procedures and reporting of results and abnormal findings can be found in the central laboratory manual.

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

Protocol-Required Laboratory Assessments

Laboratory Assessments	Variables
Hematology	Hemoglobin Hematocrit Erythrocyte count Platelet count Leukocyte count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A white blood cell (WBC) evaluation may include any abnormal cells, which will then be reported by the laboratory. A red blood cell (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	Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Total and direct bilirubin Creatinine Sodium, potassium Glomerular filtration rate, using the Modification of Diet in Renal Disease formula Thyroid hormones: Free and total triiodothyronine (T3) Free and total thyroxine (T4) Thyroid stimulating hormone (TSH)
Other Tests	A serum pregnancy test for women of childbearing potential (WOCBP) will be performed at Screening. Urine pregnancy tests will be performed at randomization and monthly thereafter (see Schedule of Activities). Urine pregnancy tests are either performed on-site during a scheduled visit or at home with the pregnancy test validated kit provided by the site. The results of the urine pregnancy tests will not be collected in the eCRF. Results of pregnancy tests will be documented in the participant's records (pregnancy test card). The date of the urine pregnancy test reported on the pregnancy card will be collected in the eCRF. Additional serum or urine pregnancy tests may be performed, if pregnancy is suspected during the study, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. NT-proBNP will be analyzed as part of the efficacy assessments (see Section 8.2.2.7).

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on GCP, and applicable regulatory and country-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 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.

During the study, in situations where a departure from the protocol is unavoidable, 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, 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 Selection

This study will only be conducted in those countries 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 10.3, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 10.3.

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.

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. 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, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to re-contact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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 consent has been obtained, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new 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.

Note, 2 ICFs will be prepared: one main ICF and one for the optional biomarker sample collection.

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 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 consent also addresses the transfer of the data to other entities and to other countries.

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. 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.

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.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Plasma and serum samples will be used to analyze fibrosis and disease-related biomarkers (see Section 8.5). 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 SAPH and pulmonary fibrosis, to provide a biological assessment of the response of participants to treatment with selexipag, to understand differential intervention responders, to determine if the markers can be used to classify participants as potential responders prior to treatment, and to develop tests/assays related to selexipag and SAPH and pulmonary fibrosis. The research may begin at any time during the study or the post-study 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 (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Sponsor Data Monitoring Committee (DMC)

A sponsor DMC has overall responsibility for safeguarding the interests of participants by monitoring safety data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring the study is conducted with the highest scientific and ethical standards.

The sponsor DMC will be fully operational prior to enrollment of the first participant into the study.

This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

Steering Committee

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

Clinical Event Committee

The Clinical Event Committee (CEC) is a sub-committee of the SC. The CEC is responsible for reviewing and adjudicating potential clinical worsening events in a blinded fashion.

CEC membership and responsibilities, as well as the adjudication procedure will be described in the CEC charter.

Participant cases will be submitted to the CEC if at least one of the following conditions is reported by the investigator:

- Hospitalization

- Increase (ie, worsening) in WHO FC
- Initiation of PH-specific medication.

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 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 substudy 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.

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 start of the study, periodic monitoring visits by the sponsor, and electronic transfer of clinical laboratory data (including NT-proBNP from a central laboratory), ePRO, and data collected by actigraphy and IRT vendor to the sponsor. 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.

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 the 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.

eCRF data will be captured via electronic data capture (eDC). The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features. A

complete electronic audit trail will be maintained. The investigator/delegate will approve the data using an electronic signature.

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.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

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

If necessary, queries will be generated in the eDC tool. If corrections to the 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.

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 variables 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 start of the study and will be described in the monitoring guidelines (or other equivalent document).

Entries recorded through an electronic device by the participant in the PROs and by the investigator, the actigraphy device and electronically transferred clinical laboratory data (including NT-proBNP from a central laboratory) and data collected by IRT are considered source data.

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:

- Referral letter from treating physician or

- Complete history of medical notes at the site or
- Discharge summaries

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 utilized, 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. These data are electronically extracted for use by the sponsor. If eSource is utilized, 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.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, or 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 data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. 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.

Detailed information is available in the study-specific monitoring guidelines.

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.

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.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the **study start date.**

Study 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: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE 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 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 Section 8.4.1 for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU 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 AE 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 (see Section 8.4).

Adverse Event Associated with the use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is related by the definitions listed below (see Attribution Definitions).

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.

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).

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 6.8)

- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

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.

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 (see Section 8.4.1). 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including OL 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 staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

Refer to Section 8.4.1 for more information on the reporting procedures of SAEs.

All SAEs that have not resolved at time of the EOS visit (see Section 4.4.1) 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 7.3])

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 in a secure manner electronically or by facsimile (fax).

PRODUCT QUALITY COMPLAINT HANDLING

Definition

A product quality complaint (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.

A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues 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 8.4.4, Pregnancy and Appendix 5: 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 men or women must 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 must 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 must 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 must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b. Male condom and female condom must not be used together (due to risk of failure with friction).

Pregnancy During the Study

If a participant becomes pregnant while on study intervention, study intervention must be discontinued and the investigator should arrange for specific therapy, as needed (Regitz-Zagrosek 2011). For reporting of pregnancies, refer to Section 8.4.4.

10.6. Appendix 6: WHO Function 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 (RHF). Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

10.7. Appendix 7: PAH-SYMPACT™ Questionnaire

Pulmonary **A**rterial **H**ypertension-**Sym**ptoms and Im**pact (PAH-SYMPACT®)** Questionnaire[a]

Programming note: Day 1 (First day of diary completion- Symptoms items only)

INSTRUCTIONS

Each day you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms.**

On the 7th day you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

Programming note: Days 2-6 (Subsequent days prior to last day in week- Symptoms items only)

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms.**

Please do not skip any questions. There are no right or wrong answers to any of the questions.

Programming note: Day 7 (Last day of week- Symptoms and Impact items)

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

a. [a] **PAH-SYMPACT®** Version 1.0, 07June2016. **PAH-SYMPACT®** is a registered trademark of Actelion Pharmaceuticals Ltd.

SYMPTOMS

1. In the past 24 hours …

   Did you use oxygen?
   ☐$_0$ No
   ☐$_1$ Yes If yes: How many hours? _____

Answer the questions that follow based on your experiences **regardless of whether you were using oxygen or not.**

2. In the past 24 hours …

   How would you rate your **shortness of breath**?
   ☐$_0$ No shortness of breath at all
   ☐$_1$ Mild
   ☐$_2$ Moderate
   ☐$_3$ Severe
   ☐$_4$ Very Severe

3. In the past 24 hours …

   How would you rate your **fatigue**?
   ☐$_0$ No fatigue at all
   ☐$_1$ Mild
   ☐$_2$ Moderate
   ☐$_3$ Severe
   ☐$_4$ Very Severe

4. In the past 24 hours …

   How would you rate your **lack of energy**?
   ☐$_0$ No lack of energy at all
   ☐$_1$ Mild
   ☐$_2$ Moderate
   ☐$_3$ Severe
   ☐$_4$ Very Severe

5. In the past 24 hours …

   How would you rate the **swelling in your ankles or legs**?
   ☐$_0$ No swelling in ankles or legs at all
   ☐$_1$ Mild
   ☐$_2$ Moderate
   ☐$_3$ Severe
   ☐$_4$ Very Severe

6. In the past 24 hours …

   How would you rate the **swelling in your stomach area**?
   ☐0 No swelling in stomach area at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

7. In the past 24 hours …

   How would you rate your **cough**?
   ☐0 No cough at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

8. In the past 24 hours …

   How would you rate your **heart palpitations (heart fluttering)**?
   ☐0 No heart palpitations (heart fluttering) at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

9. In the past 24 hours …

   How would you rate your **rapid heartbeat**?
   ☐0 No rapid heartbeat at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

10. In the past 24 hours …

    How would you rate your **chest pain**?
    ☐0 No chest pain at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

11. In the past 24 hours …

    How would you rate your **chest tightness**?
    ☐0 No chest tightness at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

12. In the past 24 hours …

How would you rate your **lightheadedness**?
☐0 No lightheadedness at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

IMPACTS

For the following questions, please select the answer that best describes how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS.** Answer the questions based on your experiences regardless of whether you were using oxygen or not.

1. In the past 7 days …

   Were you able to **walk slowly on a flat surface**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

2. In the past 7 days …

   Were you able to **walk quickly on a flat surface**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

3. In the past 7 days …

   Were you able to **walk uphill**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

4. In the past 7 days …

   Were you able to **carry things**, such as bags or baskets?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

5. In the past 7 days …

   Were you able to **do light indoor household chores**, such as preparing food, cleaning surfaces, or tidying up?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

6. In the past 7 days …

   Were you able to **wash or dress yourself**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

7. In the past 7 days …

   How much did you **need help from others**?
   ☐0 Not at all
   ☐1 A little bit
   ☐2 Some
   ☐3 Quite a bit
   ☐4 Very much

8. In the past 7 days …

   Were you able to **think clearly**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

9. In the past 7 days …

   How **sad** did you feel?
   ☐0 Not at all
   ☐1 A little bit
   ☐2 Somewhat
   ☐3 Very
   ☐4 Extremely

10. In the past 7 days …

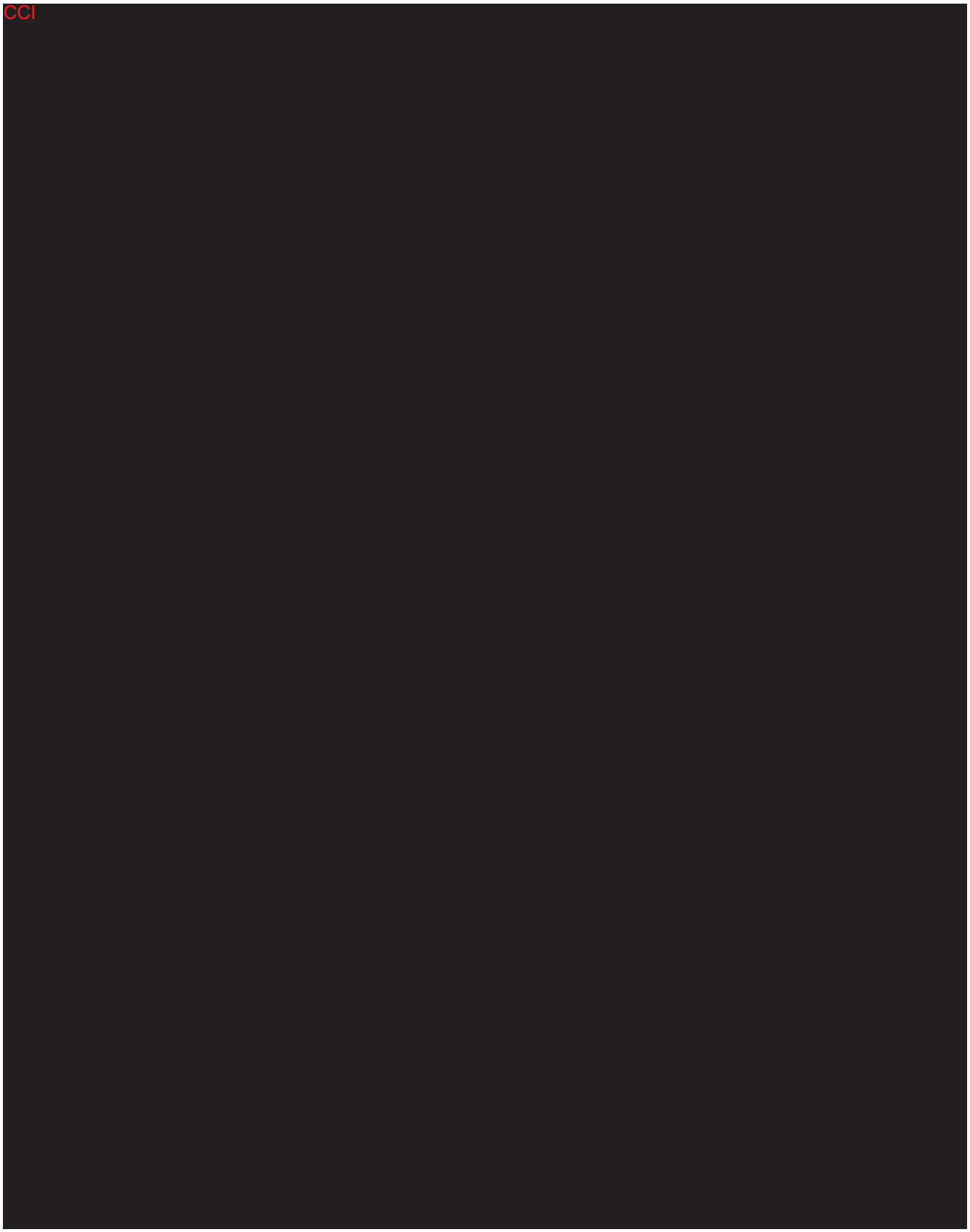
    How **worried** did you feel?
    ☐0 Not at all
    ☐1 A little bit
    ☐2 Somewhat
    ☐3 Very
    ☐4 Extremely

11. In the past 7 days …

    How **frustrated** did you feel?
    ☐0 Not at all
    ☐1 A little bit
    ☐2 Somewhat
    ☐3 Very
    ☐4 Extremely

10.8. Appendix 8: SF-12

CCI



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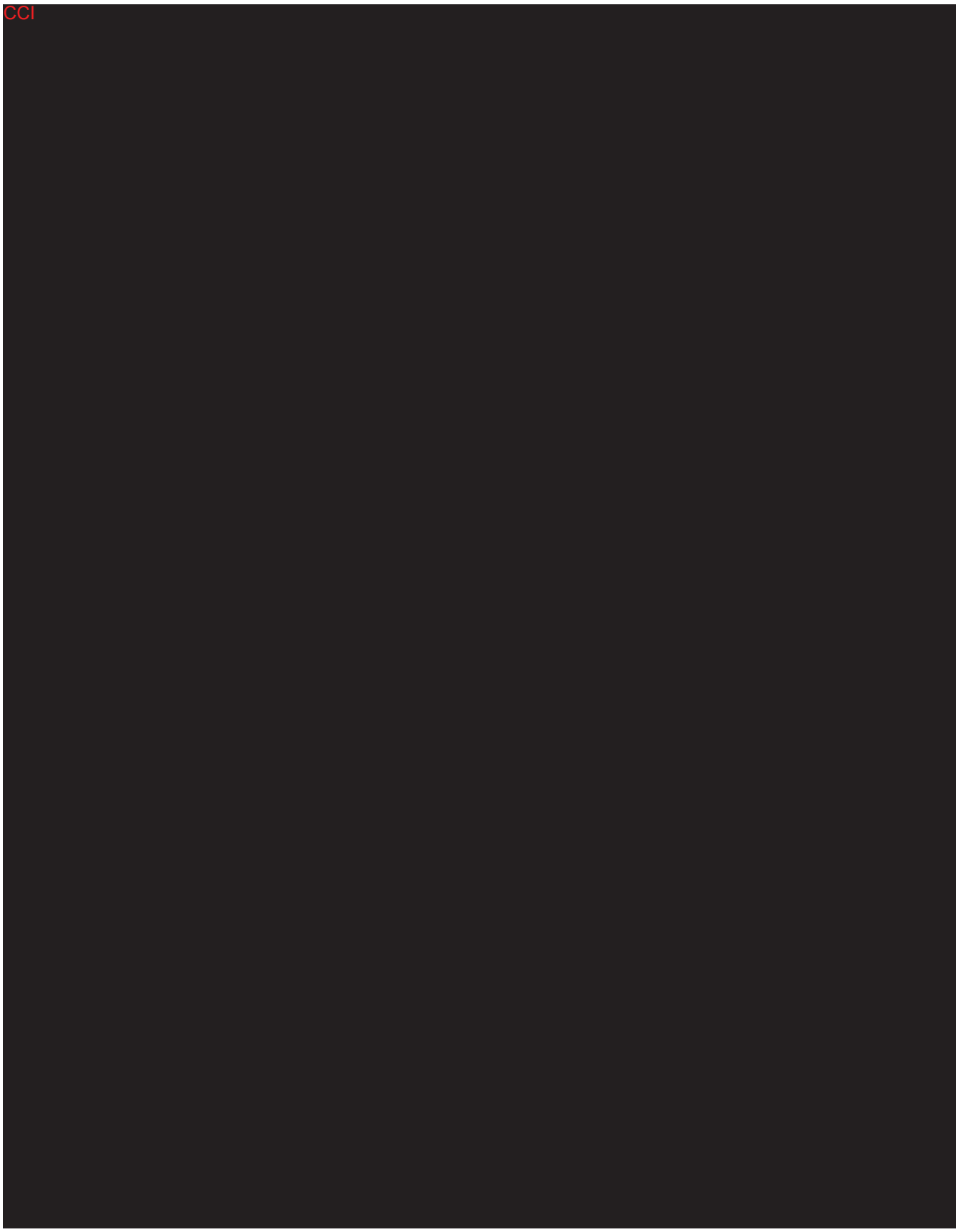

CCI

[redacted]

CCI

10.9. Appendix 9: King's Sarcoidosis Questionnaire

King's Sarcoidosis Questionnaire

This questionnaire is designed to assess the impact of sarcoidosis on various aspects of your life. Read each question carefully and answer by SELECTING the response that best applies to you. Please answer ALL questions as honestly as you can. This questionnaire is confidential.

All questions relate to how SARCOIDOSIS has affected your health.

GENERAL HEALTH STATUS

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
1	I have felt frustrated	1	2	3	4	5	6	7
2	I have had trouble concentrating	1	2	3	4	5	6	7
3	I have lacked motivation	1	2	3	4	5	6	7
4	I have felt tired	1	2	3	4	5	6	7
5	I have felt anxious	1	2	3	4	5	6	7
6	I have felt aches and pains in my muscles/joints	1	2	3	4	5	6	7
7	I have felt embarrassed	1	2	3	4	5	6	7
8	I have worried about my weight	1	2	3	4	5	6	7
9	I have worried about my sarcoidosis	1	2	3	4	5	6	7

	In the last 2 weeks...	A huge amount	A considerable amount	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
10	Tiredness has interfered with my normal social activities such as going out with friends/family	1	2	3	4	5	6	7

LUNGS

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
11	My cough has caused pain/discomfort	1	2	3	4	5	6	7
12	I have been breathless climbing stairs or walking up slight inclines	1	2	3	4	5	6	7
13	I have had to take deep breaths, also known as ‘air hunger’	1	2	3	4	5	6	7
14	My chest has felt tight	1	2	3	4	5	6	7
15	I have had episodes of breathlessness	1	2	3	4	5	6	7
16	I have experienced chest pains	1	2	3	4	5	6	7

MEDICATION

	In the last 2 weeks...	A huge amount	A considerable	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
17	I have worried about the side effects of my medication for sarcoidosis	1	2	3	4	5	6	7
18	I have felt worse because of my medication	1	2	3	4	5	6	7
19	**I have gained weight because of my medication**	1	2	3	4	5	6	7

SKIN

	In the last 2 weeks...	A huge amount	A considerable amount	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
20	I have been bothered by my skin problems	1	2	3	4	5	6	7
21	I have been concerned about changes in the color of my skin lesions	1	2	3	4	5	6	7

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
22	I have been embarrassed about my skin	1	2	3	4	5	6	7

EYES

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
23	I have had dry eyes	1	2	3	4	5	6	7
24	**I have had difficulty with bright lights**	1	2	3	4	5	6	7
25	My eyes have been red	1	2	3	4	5	6	7

26	I have had pain in/or around the eyes	1	2	3	4	5	6	7
27	I have had difficulty reading	1	2	3	4	5	6	7

	In the last 2 weeks...	A huge amount	A considerable	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
28	I have had blurred vision	1	2	3	4	5	6	7
29	I have been worried about my eyesight	1	2	3	4	5	6	7

10.10. Appendix 10: Patient Global Assessment of Disease Severity (PGA-S)

Patient Global Assessment of Disease Severity (PGA-S)

This question refers to symptoms related to sarcoidosis and associated pulmonary hypertension. Please choose the response that best describes the severity of your disease symptoms today. (Check one response)

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

10.11. Appendix 11: Clinician Global Impression of Severity (CGI-S)

Clinician Global Impression of Severity (CGI-S)

Please choose the response that best describes the severity of the patient's sarcoidosis-associated pulmonary hypertension (SAPH) symptoms today. (Check one response)

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

10.12. Appendix 12: Clinician Global Impression of Change (CGI-C)

Clinician Global Impression of Change (CGI-C)

Please choose the response that best describes the severity of the patient's sarcoidosis-associated pulmonary hypertension (SAPH) symptoms compared to the randomization visit (Visit 2). (Check one response)

- ☐ Very Much Better
- ☐ Moderately Better
- ☐ A Little Better
- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very Much Worse

10.13. Appendix 13: Child-Pugh Classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to the following table (Child-Pugh 2012; FDA Guidance 2003).

Clinical and Lab Parameters	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 encephalopathyINR International normalized ratio *	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

INR International normalized ratio

*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.

Child Pugh class is obtained by adding score for each parameter (total points):

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

10.14. Appendix 14: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

<u>Related to protocol section 8 - Study Assessments and Procedures</u>

- When participant visits to the study site are not possible, assessments and procedures may be performed remotely (eg, by phone, telemedicine) or in-person off-site (eg, at participant's home). The study site and the sponsor will discuss and agree on the applicable assessments and procedures. In any case, the following assessments and procedures will be performed at the study site: informed consent, RHC, 6MWT / Borg CR Scale® (CR10) / SpO^2, vital signs, weight, ECG, physical examination, arterial blood gas, DL_{CO}, and spirometry.

Related to protocol sections 8.3.4 - Clinical Safety Laboratory Assessments and 8.6 - Biomarkers

- When participant visits to the study site are not possible, laboratory assessments using a suitably accredited local laboratory, or the use of home phlebotomy / home testing services may be considered.

Related to protocol section 6.2 - Study Intervention, Preparation/Handling/Storage/Accountability

- When participant visits to the study site are not possible, shipment of study intervention from the study site directly to participants (and vice versa for return of study intervention) may be considered.

Related to protocol section 10.3 - Regulatory and Ethical Considerations, Monitoring, On-Site Audits

- The sponsor may apply remote monitoring and/or remote auditing if on-site visits are not possible.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

- Study participants can undergo a COVID-19 vaccination procedure in compliance with applicable local governmental regulations.
- No pharmacokinetic interaction between the study intervention and currently available COVID-19 vaccines are expected. In addition, based on the mechanism of action of the study intervention and COVID-19 vaccines, no relevant interaction is expected.
- Any COVID-19 vaccine administered to a study participant is considered a concomitant medication and should be reported on the eCRF.
- For SAEs reported after COVID-19 vaccination, the investigator should provide narrative details on the SAE form to allow adequate assessment of causal relationship between the reported SAE and vaccination. This is particularly relevant in cases where the reported SAE is an expected event with the study intervention and the COVID-19 vaccine. If the event is serious and considered to be related to both the COVID-19 vaccine and the study intervention, it is a serious adverse reaction and expectedness must be assessed. Suspected unexpected serious adverse reaction (SUSAR) reporting will be performed if the serious adverse reaction is unexpected as per applicable reference safety document.
- Study participants do not require unblinding of the study intervention to receive a COVID-19 vaccine.

10.15. Appendix 15: Protocol Amendment History

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

Amendment 2 (21-Sep-2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to clarify the Child-Pugh assessments as needed for Exclusion Criterion #13, add a Coronavirus Disease 2019 (COVID-19) appendix, adapt internal safety reporting processes, align with TransCelerate template, make minor corrections, and perform editorial document formatting revisions.

Section Number and Name	Description of Change	Brief Rationale
Summary of Changes Table (Amendment 1): Throughout the protocol	Updated text in Brief Rationale: (deleted text as strikethrough and new text in bold) To explore safety and efficacy data that require a longer observation period such as time to clinical worsening (TTCW) or long-term safety in a controlled manner, all participants, whether or not on treatment, will continue in a double blind (DB) fashion until ~~approximately 5 months after the last participant has completed the Week 39 visit (time of primary analysis results available and unblinding).~~ End of main observation period **(EOMOP) (EOMOP visit is 39 weeks [±1 month] after randomization of the last participant). Participants who do not prematurely discontinue study intervention will continue taking study intervention (DB) until the results of the analysis Timepoint 1 are available (approximately 5 months).**	As described in protocol Section 1.1 (Synopsis) and Section 7.1 (Discontinuation of Study Intervention), all participants whether or not on treatment, will continue in a DB fashion until EOMOP (EOMOP visit is 39 weeks [±1 month] after randomization of the last participant). Participants who do not prematurely discontinue study intervention before EOMOP will continue taking study intervention (selexipag or placebo) during the DB extension period. The DB extension period starts in the evening of the day of the EOMOP visit and ends with the EOT visit. This period will last approximately 5 months until the results of the Analysis Timepoint 1 are available. Participants who prematurely discontinue study treatment before EOMOP will not enter the DB extension period.
Summary of Changes Table (Amendment 1): Section 3 Objectives and Endpoints, Hypothesis	Modified the following text in Brief Rationale: (deleted text as strikethrough and new text in bold) Given the limitations in sample size to explore TTCW in a controlled manner, a longer observation period is required and all participants, whether or not on treatment, will continue in a DB fashion ~~until approximately 5 months after the last participant has completed the Week 39 visit~~ **until EOMOP (EOMOP visit is 39 weeks [± 1 month] after randomization of the last participant).**	All participants, whether or not on treatment, will continue in a DB fashion until EOMOP, to explore TTCW in a controlled manner for a longer observation period.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.1 Visits and assessments while taking double-blind study intervention	The schedule of visits indicated that study intervention dispensing/return is applicable at the scheduled telephone call Week 52 and the 6-monthly telephone calls thereafter, which was deleted.	This was incorrect, no study intervention dispensing/return will be done at telephone calls.
Section 1.3.2 Visits and assessments after premature discontinuation of study intervention	Deleted 'before EOMOP' from the title. Footnote 'a' was updated: (deleted text as strikethrough and new text in bold) ~~The premature EOT visit is the first visit after premature discontinuation of study intervention. For~~ Participants who **discontinue study intervention and have their premature EOT visit before the EOMOP visit** will ~~and~~ continue with visits and assessments **until the EOMOP visit**. If the premature EOT visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated.	The change was made to footnote to cover any premature discontinuation of study intervention, whether before or after EOMOP.
Section 4.2 Scientific Rationale for Study Design: Rationale for Right Heart Catherization	Modified the following text: (deleted text as strikethrough and new text in bold) The ~~MM~~risk associated with RHC procedures is considered acceptable for this study as it is reported to be low in centers experienced in treating PH patients and performing RHC. In addition, a historical RHC is allowed for all participants~~in the non-hemodynamic cohort and for participants in the hemodynamic cohort, if the historical RHC~~ if it was performed in accordance with the guidance provided in Section 8.2.1.1	The cohorts were previously removed in Amendment 1. This wording was overlooked at that time and is now deleted.
Section 5.1 Inclusion Criteria	Criterion #7 was updated to: (deleted text in strikethrough, and new text in bold). ~~No treatment with PH specific therapies or oral PH specific monotherapy~~ **Either not receiving PH-specific treatment, or receiving** ~~treatment with~~ **PH-specific oral monotherapy** (ie, riociguat or PDE5i or ERA); if on oral PH-specific monotherapy ~~then~~ treatment ~~had~~ has to be stable (ie, no introduction of new therapies or changes in dose) ~~during~~ for at least	The criterion was potentially misleading and based on a request from the Canadian health authority the inclusion criterion was rephrased.

Section Number and Name	Description of Change	Brief Rationale
	90 days prior to **both the RHC qualifying for enrollment and** randomization ~~and the RHC qualifying for enrollment~~.	
Section 5.1 Inclusion Criteria	Criterion #8 was updated to: (deleted text in strikethrough, and new text in bold). Stable sarcoidosis treatment regimen, ie, no new specific anti-inflammatory treatment for sarcoidosis for at least 90 days, and stable dose(s) for at least 30 days prior to **both the RHC qualifying for enrollment and** randomization ~~and the RHC qualifying for enrollment~~	For consistency, as the qualifying RHC is always before randomization.
Section 5.2 Exclusion Criteria	Criterion #6 was updated to: (deleted text in strikethrough, and new text in bold). Decompensated cardiac failure ~~if not under close supervision~~ **not receiving optimal medical treatment according to local guidelines**.	To be more specific regarding which participant may be eligible despite having decompensated cardiac failure.
Section 5.2 Exclusion Criteria	Criterion #8 was updated to: (new text in bold). Implantable cardioverter defibrillator (ICD) for secondary prevention **(current or planned).**	To clarify the previous wording.
Section 5.2 Exclusion Criteria	Updated Criterion #13: Added Appendix of Child-Pugh Classification as reference to the criterion. Added a note that: **The assessment of hepatic impairment (Child-Pugh Score) must be fully documented for patients who have clinical signs and evidence (from central and/or local lab) of hepatic impairment (see Section 10.13).**	Exclusion criterion #13 was clarified for consistency in the selexipag development program to indicate that Child-Pugh scoring is only required in patients with hepatic impairment and does not apply to patients with no hepatic impairment.
Section 6.5 Concomitant Therapy	Deleted "qualifying for enrollment" and specified Week 26 for change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to RHC :(deleted text in strikethrough, and new text in bold). Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to RHC ~~qualifying for enrollmentat~~ **at Week 26.**	To correct for an oversight and exclude potential confounders for the efficacy assessment.

Section Number and Name	Description of Change	Brief Rationale
Section 7.1 Discontinuation of Study Intervention	Added the following text: **If a participant discontinues study intervention prematurely after EOMOP but before the study results are available and the treatment assignment is unblinded, he/she will be asked to return for the premature EOT visit within 7 days of last intake of study intervention and for a safety follow-up phone call 30 (+5) days after the last intake of study intervention, provided the participant's consent for this limited participation in the study has not been withdrawn.**	Clarification of the EOT and follow-up process for participants who discontinue study intervention prematurely before the EOMOP visit and do not agree to continue to perform the visits and assessments as scheduled until the EOMOP visit.
Section 7.1 Discontinuation of Study Intervention	Section was updated to: (deleted text in strikethrough). ~~Hepatic impairment occurs or is suspected. If hepatic impairment is suspected, a clinical assessment of severity (Child Pugh score) should be performed~~ **If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If a subject has developed severe hepatic impairment (Child-Pugh C) at any time during the study, the study intervention must be permanently discontinued (see Section 10.13).**	To align with the UPTRAVI label which states that use of UPTRAVI in severe hepatic impairment should be avoided.
Section 5.2 Exclusion Criteria	Criterion #15 was updated to: (deleted text in strikethrough and new text in bold). Treatment with prostacyclin, prostacyclin analogues or IP receptor agonists (ie, selexipag) ~~during~~ **within** 90 days prior to randomization and/or prior to the RHC qualifying for enrollment, except those given at vasodilator testing during RHC.	To clarify the previous wording.
Section 6.8 Treatment of Overdose	Text moved from Section 8.5. Additional overdose definition included for participants with moderate hepatic impairment or concomitantly taking moderate CYP2C8 inhibitors which requires dosing frequency reduction from twice daily to once daily. Background	Location of text adjusted to match TransCelerate template. Text adapted to match changes with internal safety reporting processes.

Section Number and Name	Description of Change	Brief Rationale
	information for overdose added. Management of overdose updated. Deleted the text 'Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.'	
Section 8 Study Assessments and Procedures; Study-Specific Materials	Deleted SAE Fax cover page from the Study-Specific Materials.	The information previously included on a separate fax cover sheet was integrated into the SAE form and thus the add-on form is not needed.
Section 8 Study Assessments and Procedures; Overview	Revised the sentence: Actual dates and times of assessments **(where applicable)** will be recorded in the eCRF.	The time is not collected for all assessments.
Section 8.2.2.3.1 6MWT	Added that: Guidelines on execution of the 6MWT will be provided in the **separate** SPHINX 6MWT guidance document.	To clarify that the guidelines on execution of the 6MWT will be a separate document.
Section 8.2.2.3.2 Daily Life Physical Activity (DLPA) and Sleep Parameters	Removed that participants will be provided with a report summarizing their individual activity levels during the study.	Patient-specific reports will not be available from the provider for this study.
Section 8.2.2.8 Patient-Reported Outcomes	Added that: The following PRO instruments will not be administered to illiterate participants and will not be administered to a participant when the instrument is not available in a language that can be easily understood and read **by the participant.**	The PRO instruments will not be administered to a participant when it is not available in a language that can be understood and read by the participant.
Section 8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Updated the description for serious adverse events.	To adapt the text to changes in internal safety reporting processes.
Section 8.4.2 Follow-up of Adverse Events and Serious Adverse Events	Updated the description for follow-up of Adverse Events and Serious Adverse Events.	
Section 8.4.4 Pregnancy	Updated the description for pregnancy and included reporting requirement for female partners of male participants.	
Section 10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Deleted the following: Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention.	Text deleted to match the TransCelerate template as criterion is only applicable for marketed products used according to the local label. As UPTRAVI is not approved for SAPH, this is removed.

Section Number and Name	Description of Change	Brief Rationale
	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 8.4.1).	
Section 10.13 Appendix 13: Child-Pugh Classification	Added Child-Pugh Classification Appendix.	To add Child-Pugh classification to assess the severity of the liver disease.
Section 10.14 Appendix 14: COVID-19 Appendix	Added COVID-19 Appendix.	The COVID-19 appendix describes potential measures to manage the impact of the COVID-19 pandemic on the study.
References	Added new literature references: Holland AE, Spruit MA, Troosters T et al. An official European R American Thoracic Society technical standard field walking tests in chronic respiratory disease. Respir J. 2014;44:1428-1446. Borg G. Borg's Perceived Exertion and Pain Scales. Champaign, II. Human Kinetics. 1998. FDA 2003. Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003. Child-Pugh. In: Vincent JL., Hall J.B. (eds) Encyclopedia of Intensive Care Medicine. Springer, Berlin, Heidelberg. (2012). Numbering for further references were updated.	The Borg CR10 scale is newly introduced as a tool in this study. Added citations (literature references) to support the respective sections.
Section 4.1 Overall Design Section 8.2.2.3.1 6MWT Section 8.2.2.5 Dyspnea (Pre- and Post-6MWT) Section 8.2.2.6 WHO FC Section 8.2.2.8.1 PAH-SYMPACT™ questionnaire Section 8.2.2.8.2 SF-12	Added citations (literature references) to support the respective sections. References to IB addendum added.	
Section 10.1 Appendix 1: Abbreviations and Trademarks	The Abbreviations list and Definition of Terms were updated.	
Throughout the protocol	Minor editorial and document formatting revisions.	

Amendment 1 (5 December 2019)

Overall Rationale for the Amendment:

The sponsor has revised the study design following Health Authority (HA) feedback that recommended that the study should also be powered for clinical endpoints such as time to clinical worsening, 6-minute walk distance (6MWD) and patient reported outcomes (PRO). However, there is an absence of conclusive data for the effects of selexipag in patients with sarcoidosis-associated pulmonary hypertension (SAPH) to guide the design of such a study. Therefore, in agreement with the Steering Committee, the sponsor has decided to revise the scope to an exploratory Phase 2 study to investigate the effects of selexipag on hemodynamics, other efficacy endpoints, and on safety in patients with SAPH. Consequently, elements of the study design, sample size, secondary and exploratory objectives and endpoint definitions, requirements for safety monitoring and statistical considerations have been amended.

Section number and Name	Description of Change	Brief Rationale
Cover page Synopsis Section 1.3 Schedule of Activities Section 4.1 Overall Design, Section 4.2 Scientific Rationale for Study Design Section 4.4 EOS Definition Section 5 Study Population Section 6.1.3.1 Study Intervention Up-titration Section 7.1 Discontinuation of Study Intervention Section 8 Study Assessments and Procedures	The study title, study phase, study periods, visit schedule and assessments, and number of participants were changed.	This is in accordance with HA feedback which recommended that the study should be powered for clinical endpoints such as time to clinical worsening, 6-minute walk distance (6MWD) and patient-reported outcome (PRO). However, as there is an absence of conclusive data for the effects of selexipag in patients with SAPH, in agreement with the Steering Committee (SC) the sponsor decided to revise the scope to an exploratory Phase 2 study investigating the effects of selexipag on hemodynamics, other efficacy endpoints, and on safety in patients with sarcoidosis-associated pulmonary hypertension (SAPH).
Cover page and throughout the document	The study acronym (PHASE) was changed to SPHINX.	The acronym has been changed due to copyright reasons.
Throughout the protocol	All references to double-blind (DB) and open-label (OL) study intervention as well as to the two cohorts and the OL period have been removed. The term ‘study intervention’ is used to refer to DB intervention (placebo or selexipag).	The revised study design does not include an OL period. To explore safety and efficacy data that require a longer observation period such as time to clinical worsening (TTCW) or long-term safety in a controlled manner, all participants, whether or not on treatment, will continue in a DB fashion until approximately 5 months after the last participant has completed the Week 39 visit (time of primary analysis results available and unblinding). Continued treatment with study-intervention until the study results are available will allow collection of additional safety data so that investigators can make an informed decision on post-study therapy based on the study results (risk-benefit of selexipag in SAPH) and the actual treatment received by the study participants.
Section 1.3 Schedule of Activities	Instead of providing only one schedule of activities	As participants who discontinue from study intervention before the End of Main Observation

Section number and Name	Description of Change	Brief Rationale
	applicable to all participants whether or not on study intervention, a separate schedule of activities for participants who prematurely discontinue study intervention is provided in Section 1.3. Footnotes were changed accordingly.	Period (EOMOP) visit should continue with all visits and assessments up to the EOMOP, separate schedules of activities are provided for participants on study intervention (Section 1.3.1) and for participants who prematurely discontinued study intervention (Section 1.3.2.
Section 3 Objectives and Endpoints, Hypothesis	Pulmonary vascular resistance (PVR) assessment and analysis changed from Week 20 to Week 26. Assessment and analysis of other clinical endpoints, including daily life physical activity and PROs changed from up to Week 52 to up to Week 39. TTCW will be analyzed up to EOMOP instead of up to Week 52.	The timepoint of the assessment of the primary endpoint PVR has been moved from Week 20 to Week 26 for consistency with the timeframe for repeated/follow-up right heart catheterization (RHC) in clinical practice. Other clinical endpoints, such as daily life physical activity and PROs will be assessed and analyzed up to Week 39 to explore the correlation between the effect of study intervention on cardiopulmonary hemodynamics (change in PVR up to Week 26) and its translation into clinical and functional changes over time. Given the limitations in sample size to explore TTCW in a controlled manner, a longer observation period is required and all participants, whether or not on treatment, will continue in a DB fashion until approximately 5 months after the last participant has completed the Week 39 visit.
Section 3 Objectives and Endpoints	All secondary and exploratory objectives are grouped under exploratory objectives, and the wording was revised as necessary to match the study objective and analysis plan. Assessment of daily life physical activity (DLPA) and sleep parameters up to Week 39 (DLPA) by actigraphy were added.	Given the limitation in sample size in this rare indication, no secondary endpoints are defined for which hypotheses are tested with adequate control of type I error. All efficacy endpoints other than PVR are exploratory, and only a brief general description on the planned analyses are described in the protocol. Full details will be provided in the Statistical Analysis Plan. Assessment of DLPA and sleep parameters was added to explore as a novel endpoint in SAPH patients.
Throughout the document	The requirement for collection of medical resource utilization data has been removed.	In line with the revised study strategy, collection of this information is not required.
Throughout the document	All reference to HRCT (High-resolution computed tomography) and cardiac MRI are removed, including related inclusion and exclusion criteria.	To reduce the burden for participants, the HRCT and cardiac MRI substudies have been removed.
Section 2.3.5 Overall Benefit/Risk Assessment	Independent Data Monitoring Committee	Protocol Version 2 does not include decision-making based on interim analysis. Thus, in line

Section number and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 6.3 Measures to Minimize Bias – Randomization and Blinding Section 9.5.2.1 Study Safety Monitoring Section 9.6 Data monitoring Committee Appendix 3 Committees Structure	(IDMC) responsibilities are now covered by the sponsor's Data Monitoring Committee (DMC).	with the company requirements for a DMC in a non-confirmatory study, and in agreement with the SC, an IDMC is not required. To ensure participants' safety as well as data quality, the safety information will be monitored and reviewed on a continuous basis by a sponsor DMC not otherwise involved in the conduct of the study, rather than by an IDMC.
Section 9 Statistical Considerations	The sample size was reduced from 150 to 74 due to the removal of the interim analysis rules. The primary estimand was changed from a treatment policy estimand to a "while on-treatment" estimand. The HRCT Analysis Set (HAS), Cardiac MRI Analysis Set (MAS) and Selexipag-Initiated Set (SIS) analysis populations were removed, and the Hemodynamic Set (HS) set was replaced by the Full Analysis Set (FAS), which was updated from "All participants assigned to study intervention" to "All randomized patients who took at least one dose of study intervention and for whom a valid baseline PVR value could be obtained". The detailed analysis plan and sample size considerations for the secondary endpoints was removed and substituted with a high-level plan for the analysis of the "other efficacy endpoints".	With the removal of the initially planned interim analysis on PVR for futility and with TTCW becoming an exploratory endpoint, the required total sample size is reduced to 74 participants; the study will be adequately powered for analysis of the primary efficacy endpoint (PVR) as per the original assumptions. The analysis timepoints are revised to match the study design modifications.
Section 8.2.2.3.1 6MWT	Requirements for the length of the corridor for the 6-minute walk test (6MWT) were removed and will be included in the separate guidance document separate to the protocol.	For consistency with company requirements for the 6MWT.
Section 3 Objectives and Endpoints	The endpoint: *Change from baseline in forced*	As per SC recommendation.

Section number and Name	Description of Change	Brief Rationale
	vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DL_{CO}) was moved from exploratory to safety endpoints.	
Section 3 Objectives and Endpoints Section 8.3 Safety Assessments Section 1.3 Schedule of Activities	Monitoring of arterial blood gas (ABG) was added as a safety assessment.	As per SC recommendation.
Section 3 Objectives and Endpoints Section 8.2.2.1 Clinical Worsening and Hospitalization	The definition of clinical worsening (CW) components is modified to include all-cause death, non-planned pulmonary hypertension (PH)-related hospitalization, increase in WHO functional class (FC), lung transplantation, atrial balloon septostomy and initiation of parenteral or new class of PH-specific therapy for clinical worsening.	Following the SC recommendation, the CW component definition has been refined to better reflect relevant determinants of CW events in patients with SAPH, and also requires adjudication.
Section 4.1 Overall Design Section 8.2.2.1 Clinical Worsening and Hospitalization Appendix 3 Committees Structure	Addition of a clinical event committee (CEC) responsible for adjudication of cases, ie, hospitalization, increase in WHO FC and initiation of new PH-specific therapy.	To better reflect relevant determinants of CW in patients with SAPH the components for the TTCW endpoint were refined based on the recommendation of the SC. A sub-committee of the SC will serve as the CEC responsible for adjudication of CW events.
Section 5.1 Inclusion criteria Section 6.5 Concomitant Therapy	Inclusion criterion 7 regarding PH-specific therapy was reworded to clarify that only PH-specific monotherapy (ie, endothelin receptor antagonist or phosphodiesterase type-5 inhibitor or riociguat) is allowed for inclusion. Section 6.5 concomitant medications was modified accordingly.	To be able to understand the treatment effect resulting from selexipag treatment it is important to reduce any confounding factors, ie, concomitant PH-specific therapies. Therefore, SAPH patients who are receiving combination PH-specific therapy are not eligible.
Section 8 Study Assessments and Procedures	The 6MWT starter kit will not be provided by default to all sites.	Only sites experienced and equipped for performing the 6MWT will be selected for this study. As part of the site selection it will be assessed if any materials/equipment needs to be provided by the sponsor.
Appendix 6 Appendix 7 Appendix 8	Information provided in Appendix 6 (RHC), Appendix 7 (6MWT) and	To allow for dedicated training (other than protocol training) and documentation of these for

Section number and Name	Description of Change	Brief Rationale
References to the appendices throughout the protocol	Appendix 8 (Borg Dyspnea Index scale) were removed from the protocol and will instead be provided as separate guidance documents outside of the protocol. All references to these appendices were removed.	study personnel involved in performing the RHC and 6MWT.
Section 5.1 Inclusion Criteria	Inclusion criterion #5, eligibility requirements for the PVR value was modified from PVR ≥240 dyn*sec/cm^5 (≥3 WU) to PVR ≥320 dyn*sec/cm^5 (≥4 WU).	To ensure recruitment of participants with substantially impaired pulmonary vascular function.
Section 5.1 Inclusion Criteria	Inclusion criteria #10 and #11 regarding forced expiratory volume criteria were adjusted.	Following the SC recommendation to exclude patients with moderate and severe pulmonary obstruction and restriction.
Section 5.2 Exclusion criteria	Addition of a new exclusion criterion (# 27) to clarify that pregnant women are not allowed to participate in this study.	Added for clarity at the request of the UK Ethics Committee.
Appendix 5 Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Bilateral tubal ligation/occlusion was removed from the definition of a woman being of non-child-bearing potential. Therefore, women who have undergone bilateral tubal ligation/occlusion are considered to be of childbearing potential.	Bilateral tubal ligation/occlusion is not considered a method of permanent sterilization as it is potentially reversible. Bilateral tubal ligation/occlusion is included in the list of acceptable methods of contraception.
Appendix 5 Contraceptive and Barrier Guidance and Collection of Pregnancy Information – Examples of Acceptable Contraceptives in this Study	Bilateral tubal occlusion/ligation procedure was removed from the definition of a woman being not of childbearing potential. Bilateral tubal occlusion/ligation are acceptable methods of contraception.	Bilateral tubal occlusion/ligation procedure is potentially reversible, therefore these women will still be considered as of childbearing potential.
Section 5.4 Screen Failures	Re-screened participants will be assigned a different participant number than for the initial screening.	Internal sponsor decision: screen-failed participants will be assigned a new participant number in case of re-screening
Section 8 Study Assessments and Procedures	Optional patient experience survey was removed.	Participant feedback from different clinical trials was gathered and used to improve the design and conduct of future trials. Meanwhile, sufficient

Section number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities − Qualitative Interviews Appendix 3 Data Quality Assurance and Source Documents		information was collected from enough studies for its primary purpose. The conduct of further similar surveys for new studies is not required, as it would increase the burden for participants.
Section 6.4 Study Intervention Compliance	It was clarified that compliance calculated by study personnel is to be documented in the source documents.	Clarification of requirements for expected source data documentation.
Section 8 Study Assessments and Procedures − Table 2 and associated text − Volume of Blood to be Collected from Each Participant per Visit	Required amount of blood adjusted due to removal of the OL period. Provision made for 1 mL to 3 mL and 2 mL of blood to be collected for cardiac output (CO) according to Fick's method and ABG, respectively.	Removal of the OL period decreased the amount of blood required to be collected. Some labs may use Fick's method for the calculation of CO during RHC. This and ABG would require additional collection of approximately 1 mL to 3 mL and 2 mL of blood, respectively.
Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.	Minor errors were noted and corrected.

11. REFERENCES

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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 course of 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	25-Feb-2022 14:36:08 (GMT)	Document Approval
PPD	25-Feb-2022 17:41:26 (GMT)	Document Approval