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

Clinical Protocol

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

SOMBRERO

Protocol 67896049PUH3001; Phase 3b, Amendment 2

JNJ-67896049 / ACT-293987 (selexipag)

* Actelion Pharmaceuticals Ltd. ("Actelion") is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Actelion studies may vary, such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

IND: 104504
EudraCT NUMBER: 2020-000475-21

Status:	Approved
Date:	26 October 2021
Prepared by:	Actelion Pharmaceuticals Ltd. and Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-RIM-265923, 2.0
Protocol Version:	3.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2, Version 3	26-Oct-2021
Amendment 1, Version 2	08-Dec-2020
COVID-19 Appendix (EDMS-RIM-272313, 1.0)	27-Nov-2020
Original Protocol, Version 1	04-Mar-2020

Amendment 2 (26 October 2021)

Overall Rationale for the Amendment: The main reason for the amendment is to clarify the definition of end of study (EOS) and safety reporting requirements for participants who complete treatment in this study and who will continue with selexipag treatment by rolling over into a post-trial access (PTA) program or Study NOPRODPAPUH3001 (PLATYPUS). This is to avoid duplicate reporting of adverse events (AEs) in the clinical databases and of serious adverse events (SAEs) in the safety database. In addition, exploratory objectives, endpoints and analyses corresponding to World Health Organisation functional class (WHO FC) and overall survival status were deleted to reflect the recent update in SOMBRERO study population that the SOMBRERO study will only recruit the participants with pulmonary arterial hypertension (PAH) from the GRIPHON OL study.

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

Section Number and Name	**Description of Change**	**Brief Rationale**
1.1. Synopsis (Objectives and Endpoints; Exploratory Evaluation; Statistical Methods-Exploratory Analyses); 1.3. Schedule of Activities (SoA); 3. Objectives and Endpoints; 4.1. Overall Design; 8.2. Exploratory Assessment; 9.4.3. Exploratory Endpoint and Analyses	Exploratory objectives, endpoints and analyses corresponding to World Health Organisation functional class (WHO FC) and overall survival status were deleted.	To reflect the recent update in study population that the SOMBRERO study will only recruit the participants with PAH from the GRIPHON OL study. As survival and WHO FC are not assessed in GRIPHON OL, these endpoints will not be included in the current study.
1.1. Synopsis (Exploratory Evaluation, Statistical Methods-Exploratory Analyses); 8.2. Exploratory Assessment; 8.2.1. Dose Reduction or Increase of Selexipag; 9.4.3. Exploratory Endpoint and Analyses	'Selexipag dose reduction or increase and corresponding reasons' was included under the heading of 'Exploratory Evaluation' or 'Exploratory Endpoints and Analyses' and sections of 'Efficacy Evaluations/Assessments' were deleted.	To align with updates corresponding to exploratory evaluations.
1.1. Synopsis (Overall Design); 1.3. Schedule of Activities (SoA): Footnote 'g'; 4.1. Overall Design	Following text was revised and added at applicable instances: '**Participants will present for the EOT visit within 7 days of the last dose of study intervention**. **For participants rolled over to post-trial access (PTA) or Study NOPRODPAPUH3001 (PLATYPUS), the enrollment**	To update information about the end of treatment (EOT) Visit / EOS Visit.

Section Number and Name	Description of Change	Brief Rationale
	must occur on the day of the last visit of SOMBRERO study, ie, EOS visit which corresponds to EOT, to avoid selexipag treatment interruption.'	
	Following text was included: '**For participants who complete the study treatment and who are eligible for a post-trial access (PTA) or Study NOPRODPAPUH3001 (PLATYPUS), the post-treatment follow-up period will be waived.**'	To clarify the reporting of AEs/SAEs after the last study drug administration in the SOMBRERO study for participants who will continue to be treated with selexipag after the end of study (EOS) Visit in a PTA program or Study NOPRODPAPUH3001 (PLATYPUS).
1.1. Synopsis (Number of Participants); 2.1. Study Rationale; 2.3.2. Benefits for Study Participation; 9.2. Sample Size Determination	Content related to rollover of participants to current study from ongoing interventional clinical studies with selexipag in various indications in other classes of pulmonary hypertension (PH) was deleted.	As the current study will only recruit the participants with PAH from the GRIPHON OL study.
1.1. Synopsis (Overall Design); 4.1. Overall Design; 8. Study Assessment and Procedures	Text was updated (deletion of '[limited] efficacy') to indicate that only safety and other information will be collected during study visits and telephone calls.	As no efficacy assessments will be performed.
1.1. Synopsis (Safety Analyses); 9.4.2. Safety Analyses	The term 'stratified by indication' was deleted.	As the current study will only recruit the participants with PAH from the GRIPHPON OL study.
1.2. Schema (Figure 1)	Abbreviations and following note were added under Figure 1: '**For participants who are entering a post-trial access (PTA) program or Study NOPRODPAPUH3001 (PLATYPUS), the enrollment must occur on the day of the last visit of SOMBRERO study ie, EOS visit which corresponds to EOT to avoid selexipag treatment interruption. The post-treatment follow-up period will be waived in this case.**'	To indicate that EOT = EOS for participants rolling over to a continued access program with selexipag.
1.3. Schedule of Activities (SoA)	Note corresponding to 'Concomitant therapy' was deleted.	As information about all concomitant medications is collected.
2. Introduction	Following statement was added: '**Unless specified otherwise, the parent study refers to GRIPHON OL throughout the protocol.**'	As the current study will only recruit the participants with PAH from the GRIPHPON OL study.
8. Study Assessments and Procedures	Following statement was deleted: '~~If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following~~	As no efficacy assessments will be performed.

Section Number and Name	Description of Change	Brief Rationale
	~~sequence: safety assessments and WHO FC.~~'	
8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events	Text updated to indicate that AEs and SAEs will be reported '**up to EOS for participants who enter a continued access program on the same day as the EOS Visit'**.	To clarify that for participants who enter a post-trial access program or Study NOPRODPAPUH3001 (PLATYPUS), safety information is to be reported up to EOS visit in this study.
10.6. Appendix 6: World Health Organization (WHO) Functional Classification of Pulmonary Hypertension	Appendix 6 was deleted and following appendices were renumbered.	As the current study will only recruit the participants with PAH from the GRIPHON OL study, WHO-FC assessment is no longer applicable.
10.7. Appendix 7: Guidance on Study Conduct During Natural Disaster	Included updates about 'Study conduct related to COVID-19 vaccine deployment for non-COVID-19 clinical trials.'	To align with Medicines and Healthcare products Regulatory Agency (MHRA) vaccination guidance to be followed during Corona Virus Disease-2019 (COVID-19) pandemic.
11. References	Reference corresponding to selexipag investigator's brochure (IB) was updated.	To update information about latest IB and IB-addendum (edition and publishing date).
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Selexipag (JNJ-67896049, also known as ACT-293987) is an oral, selective and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor) approved and commercially available for the treatment of pulmonary arterial hypertension (PAH) in the United States, European Union, Japan and other countries.

The purpose of the SOMBRERO study is 1) to enable participants of selexipag clinical studies in pulmonary hypertension who are currently treated with selexipag to continue to benefit from treatment with selexipag after the closure of their parent study in case they have no alternative means of access to selexipag (eg, commercially available drug, post-trial access program), and 2) to accrue long-term safety data on selexipag, which may be used in interactions with health agencies and in aggregate study reports.

OBJECTIVES AND ENDPOINTS

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

Hypothesis

There will be no formal statistical hypothesis testing in this study.

OVERALL DESIGN

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

The study includes 3 periods:

- a screening period starting with the signature of the informed consent form and ending with the administration of the first dose of the study intervention (all expected to take place on Day 1, which may correspond to EOT in their respective parent study).
- an open-label treatment period starting with the administration of the first dose of the study intervention and ending on the day of the last dose of study intervention (EOT). All participants entering the study will continue with the same maintenance dose of selexipag that they were taking during their respective parent study. Participants will present for the EOT visit within 7 days of the last dose of study intervention. For participants rolled over to post-trial access (PTA) or Study NOPRODPAPUH3001 (PLATYPUS), the enrollment must occur on the day of the last visit of SOMBRERO study ie, EOS visit which corresponds to EOT, to avoid selexipag treatment interruption.
- a post-treatment follow-up period starting on the day after the last dose of study intervention and ending 30 days thereafter with the EOS visit. For participants who complete the study treatment and who are eligible for a post-trial access (PTA) program or Study NOPRODPAPUH3001 (PLATYPUS), the post-treatment follow-up period will be waived.

Following enrollment, telephone calls (TCs) or regular visits with the investigator to collect safety and other information will be scheduled alternatingly every 6 months.

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

NUMBER OF PARTICIPANTS

There is no pre-determined number of participants to be enrolled in the study; it will depend on the number of participants who are taking selexipag at the end of their parent study and whether they have other options to access selexipag when their parent study is completed. The maximum number of participants currently expected to roll-over from the GRIPHON OL study is approximately 50 participants.

INTERVENTION GROUPS AND DURATION

An individual's participation in the study will last until access to selexipag (eg, commercially available drug, post-trial access program) has been identified. Consequently, the duration of the study will be different for each individual participant and will depend on the time of access to selexipag. The dose of open-label selexipag administered at the end of the parent study will be maintained in the SOMBRERO study and can be adjusted at any time during the study if the investigator identifies a tolerability/efficacy concern.

Description of Interventions

The study intervention, selexipag (JNJ-67896049), will be provided as round, film-coated tablets at all dose strengths (200, 400, 600, 800, 1,000, 1,200, 1,400 and 1,600 μg), to be taken orally twice daily (bid), in the morning and in the evening (about 12 hours apart), unless the participant needs to start treatment with a moderate cytochrome P4502C8 (CYP2C8) inhibitor concomitantly; in these cases, selexipag will be administered once daily. Dosing frequency of selexipag should be reverted to bid when co-administration of a moderate CYP2C8 inhibitor is stopped. If a participant is already receiving a moderate inhibitor of CYP2C8 at the time of study enrollment, the dosing and dosing frequency of selexipag must be considered based on medical judgment at the time of study entry and when co-administration of a moderate CYP2C8 inhibitor is stopped. If the participant develops moderate hepatic impairment (eg, Child-Pugh class B) once daily administration must be considered. Differentiation of the tablets is based on the color and a debossing according to the selexipag dose in hundreds of μg (eg, 4 for 400 μg, 12 for 1,200 μg).

SAFETY EVALUATIONS

Safety evaluations include monitoring of all AEs, SAEs, and pregnancy tests.

EXPLORATORY EVALUATION

Selexipag dose reduction or increase and corresponding reasons.

STATISTICAL METHODS

Sample Size Determination

Due to the nature and scope of this study, the sample size is not based on statistical considerations. The sample size will be driven by the number of participants still taking selexipag who do not have other options to access selexipag when their respective parent study is completed.

Safety Analyses

Descriptive summaries for all TEAEs, AEs leading to premature discontinuation of selexipag, SAEs (up to 30 days after study intervention discontinuation), and deaths using number of participants and percentage, as well as listing of pregnancies, will be provided.

Exploratory Analyses

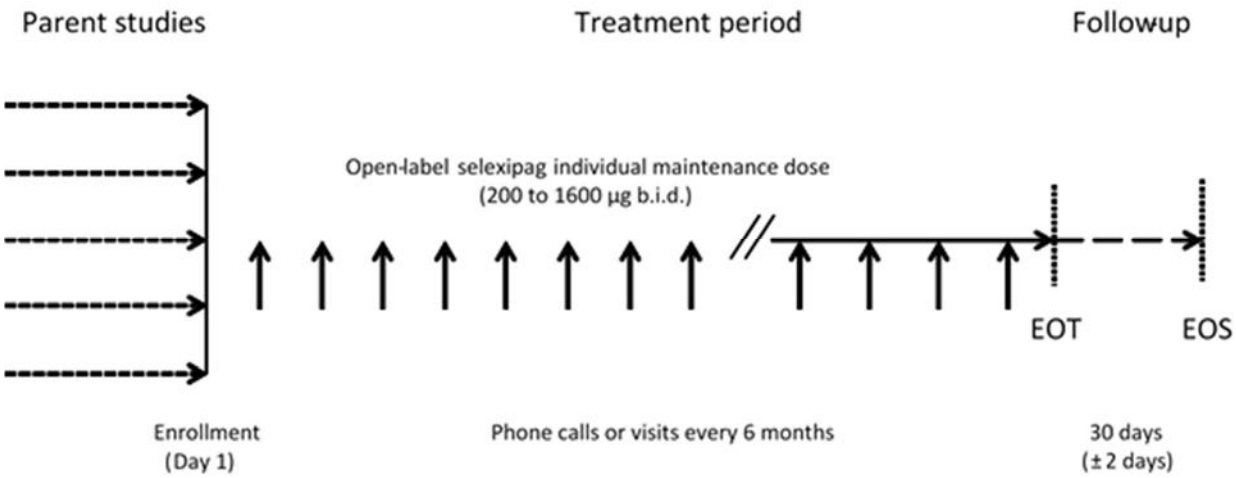
Dose reduction or increase of selexipag will be summarized descriptively, by reason.

Interim Analyses

No formal interim analysis is planned. However, data from this study may be used for interactions with health authorities and/or aggregate safety reporting. Details about such analyses will be provided in the respective statistical analysis plan (SAP).

1.2. Schema

Figure 1: Schematic Overview of the Study



EOT = end of treatment; EOS = end of study; PTA = post-trial access; OL = open-label.

Note: For participants who are entering a post-trial access (PTA) or Study NOPRODPAPUH3001 (PLATYPUS), the enrollment must occur on the day of the last visit of SOMBRERO study ie, EOS visit which corresponds to EOT to avoid selexipag treatment interruption. The post-treatment follow-up period will be waived in this case.

1.3. Schedule of Activities (SoA)

Period	Screening	Open-label Treatment					Post-treatment Follow-up	
Visit	1		2, 4, 6, etc.	3, 5, 7, etc.		U1, 2, 3, etc.		
	Screening & Enrollment		TC[a] Month 6, 18, 30, etc.	Study-site visit Month 12, 24, 36, etc.	End-of-Treatment (EOT)12[g]	Unscheduled[b]	End-of-Study (EOS)[a,g]	
Day/Month	Day 1	Monthly (±1 week)	Day 183, 547, 911, etc. (±28 days)	Day 365, 729, 1093, etc. (± 28 days)	Within 7 days after last dose	As clinically indicated	30 days (±2 days) after last dose	
Study Procedure								**Notes**
Screening/Administrative								
Informed consent	X							Must be signed before first study-related activity
Eligibility criteria[c]	X							
Participant identifier from parent study	X							
TC for pregnancy test reminder and contraception counseling		X						
Ongoing adverse events from parent study	X							
Study Intervention Administration								
Dispense study intervention	X		X[d]	X				
Study intervention accountability				X	X			
Safety Assessments[e]								
Pregnancy test[f]	X	X	X	X	X	X	X[g]	Recorded in source documents only
SAEs, AEs	←						→	
Ongoing Participant Review								
Concomitant therapy	←						→	

AE = adverse events; SAE = serious adverse events; TC = telephone call.

Footnotes:

a. To be performed by telephone by the investigator If deemed clinically indicated by the investigator, all or selected TCs may be performed as study site visits. Participants must present at the study site within the allowed time window for resupply of study intervention.

b. Unscheduled visits may be performed at any time during the study as clinically indicated. All unscheduled assessments are performed at the discretion of the investigator.

c. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

d. Study intervention re-supply visits will be scheduled every 6 months. For those months when a TC with the investigator is scheduled, the participant may pick up the re-supplies at the study site without meeting with the investigator. The TC will still be required but can be scheduled within the allowed time window.
e. Key safety assessments are listed. For special reporting situations, refer to Section 10.4, Appendix 4.
f. A urine (or serum if applicable) pregnancy test for women of childbearing potential must be performed at screening if not already performed at the last visit of the parent study. Thereafter, urine pregnancy tests will be performed at home monthly using the urine pregnancy test kits provided by the study site. A urine (or serum if applicable) pregnancy test will be performed at all study site visits.
g. For participants who complete the study treatment and who are eligible for a post-trial access (PTA) or Study NOPRODPAPUH3001 (PLATYPUS), the post-treatment follow-up period will be waived. Participants will present for the EOT visit within 7 days of the last dose of study intervention. For participants rolled over to PTA or Study NOPRODPAPUH3001 (PLATYPUS), the enrollment must occur on the day of the last visit of SOMBRERO study, ie, EOS visit which corresponds to EOT, to avoid selexipag treatment interruption.

2. INTRODUCTION

Selexipag (JNJ-67896049, also known as ACT-293987) is an oral, selective and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor) approved and commercially available for the treatment of pulmonary arterial hypertension (PAH) in the United States, European Union, Japan, and other countries.

Selexipag targets the prostacyclin pathway by selectively stimulating the IP receptor to promote vasodilation and antiproliferation. Adverse effects are similar to the prostacyclin class, including myalgia and jaw pain in addition to diarrhea. Selexipag is a substrate of CYP2C8 and is contraindicated with concomitant gemfibrozil (Coons 2019).

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

The term "study intervention" throughout the protocol, refers to study drug.

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

The term "participant" throughout the protocol refers to the common term "subject".

Unless specified otherwise, the parent study refers to GRIPHON OL throughout the protocol.

2.1. Study Rationale

The purpose of the SOMBRERO study is two-fold.

First, SOMBRERO will enable clinical study participants with pulmonary hypertension (PH) who are currently treated with selexipag to continue to benefit from selexipag after the closure of their parent study in case they have no alternative means of access to selexipag (eg, commercially available drug, post-trial access [PTA] program). SOMBRERO will only be open for indications for which a positive benefit-risk has been established and approval for market authorization is ongoing in the country of residence or approval was already granted in other countries. Currently, a positive benefit/risk profile of selexipag has been established in PAH.

Second, SOMBRERO will also accrue long-term safety data on selexipag, which may be used in interactions with health agencies or in aggregate study reports.

2.2. Background

Efficacy of selexipag was demonstrated during a long-term, double-blind, placebo-controlled, event-driven Phase 3 study conducted in 1156 PAH patients (AC-065A302, GRIPHON study). A summary of the GRIPHON study is provided below.

Participants in the GRIPHON study were randomly assigned to receive placebo or selexipag in individualized doses (maximum dose, 1,600 µg twice daily). Participants were eligible for

enrollment if they were not receiving treatment for PAH or if they were receiving a stable dose of an endothelin receptor antagonist, a phosphodiesterase type 5 (PDE-5) inhibitor, or both. The primary endpoint was a composite of death from any cause or a complication related to PAH up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo) (Sitbon 2015).

A primary endpoint event occurred in 41.6% of participants in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group compared with the placebo group, 0.60; 99% confidence interval, 0.46 to 0.78; p<0.001). Disease progression and hospitalization accounted for 81.9% of the events. The effect of selexipag with respect to the primary endpoint was similar in the subgroup of participants who were not receiving treatment for the disease at baseline and in the subgroup of participants who were already receiving treatment at baseline (including those who were receiving a combination of 2 therapies). By the end of the study, 105 participants in the placebo group and 100 participants in the selexipag group had died from any cause. Overall, 7.1% of participants in the placebo group and 14.3% of those in the selexipag group discontinued their assigned regimen prematurely because of adverse events (AEs). The most common AEs in the selexipag group were consistent with the known side effects of prostacyclin, including headache, diarrhea, nausea, and jaw pain (Sitbon 2015).

The risk of the primary composite endpoint of death or a complication related to PAH was significantly lower with selexipag than with placebo. There was no significant difference in mortality between the 2 study groups at the end of the study (Sitbon 2015).

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of selexipag may be found in the IB (Selexipag IB).

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Drug-drug interactions	Refer to the Selexipag IB.	Concomitant treatment with a strong CYP 2C8 inhibitor (eg, gemfibrozil) is prohibited until discontinuation of the study intervention (Refer to Sections 5.2 and 7.1). Dose adjustment is recommended in case of co-administration with a moderate CYP2C8 inhibitor (refer to Sections 6.1 & 6.5) or with rifampicin (Refer to Section 6.5).
Hepatic impairment	Refer to the Selexipag IB.	Exclusion of participants with severe hepatic impairment (Refer to Sections 5.2. and 7.1). Reduced dosing regimen is recommended in participants with moderate hepatic impairment (Refer to Section 6.1).
Pregnancy	Refer to the Selexipag IB.	Exclusion of pregnant and breastfeeding female participants, or female participant

		planning to become pregnant while enrolled in this study (Refer to Sections 5.2, and 7.1). The study site will contact participants for contraception counseling and as a reminder to perform the urine pregnancy tests and record the results as specified in Section 8.
Pulmonary veno-occlusive disease (PVOD)	Refer to the Selexipag IB.	Exclusion of suspected or known PVOD (Refer to Sections 5.2 and 7.1)
Risks Due to Study Intervention (selexipag)		
Prostacyclin-associated adverse events: headache, diarrhea, nausea, jaw pain, vomiting, pain in extremity, myalgia, flushing, arthralgia, and pain.	Refer to the Selexipag IB.	Dose adjustments are allowed in case of tolerability issues (Refer to Section 6.6).
Hyperthyroidism	Refer to the Selexipag IB.	Participants with uncontrolled thyroid disease are excluded (Refer to Section 5.2). Specific safety assessments may be performed as per medical advice on a case-by-case basis (Refer to Section 8.1).
Other AEs reported more frequently on selexipag compared to placebo: anemia, hypotension, nasopharyngitis, nasal congestion, decreased appetite, weight decrease, rash, urticaria, erythema	Refer to the Selexipag IB.	Appropriate measures should be taken as per local clinical practice in case of anemia and/or hypotension suspicion or manifestation (Refer to Section 8.1). Dose adjustments are allowed in case of tolerability issues (Refer to Section 6.6).
Risks Due to Study Procedures		
Possible bruising and discomfort from venipuncture if serum pregnancy tests are obtained from women of child-bearing potential	NA	Minimal blood sample collection and the option to use urine samples for pregnancy testing

2.3.2. Benefits for Study Participation

The benefit for study participation is that this study will enable participants to continue treatment with selexipag in indications for which a positive benefit-risk has been established when no other means of access is available. For PAH, a positive benefit/risk assessment has been established (Selexipag IB, Sitbon 2015). Selexipag is currently indicated for the treatment of PAH World Health Organization functional class (WHO FC) Group I to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO FC II to III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%) (Sitbon 2015).

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with selexipag are justified by the anticipated benefits that may be afforded to participants with PAH.

3. OBJECTIVES AND ENDPOINTS

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

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

There will be no formal statistical hypothesis testing in this study.

4. STUDY DESIGN

4.1. Overall Design

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

The study includes 3 periods:

- a screening period starting with the signature of the informed consent form and ending with the administration of the first dose of the study intervention (all expected to take place on Day 1 which may correspond to EOT in their respective parent study).

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

Safety assessments include monitoring of AEs, SAEs, and pregnancy tests.

Following enrollment, telephone calls (TCs) or regular visits with the investigator to collect safety and other information will be scheduled alternatingly every 6 months.

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

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

An open-label design is justified as the participants enrolled in this study will receive the study intervention at the same maintenance dose that they were receiving in their parent study.

The study is designed to include both TC and study site visits alternatively every 6 months to monitor the safety of the participants and allow for the resupply of study intervention until each participant has access to commercially available selexipag. This safety monitoring schedule is supported by the established safety profile of selexipag for daily doses up to 3,200 µg (1,600 µg twice daily [bid]).

4.2.1. Study-Specific Ethical Design Considerations

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

The total blood volume to be collected is expected to be none or minimal during this study, based on assessments to be performed according to the SoA table and Section 8.

4.3. Justification for Dose

All available dose strengths of selexipag will be supplied to maintain the participant's maintenance dose established per protocol in their parent study. The dose of selexipag may be adjusted during the study as necessary.

4.4. End of Study Definition

End of Study Definition

EOS is considered as the last scheduled study assessment shown in the Schedule of Activities (SoA) 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 EOS Visit in the time frame specified in the Clinical Trial Agreement.

EOS for an individual participant occurs when one of the following occurs:

- the participant decides to withdraw from the study or the treating physician determines it is in the best interest of the participant to withdraw from study
- the study is terminated
- the participant dies.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments through the EOS.

5. STUDY POPULATION

Screening for eligible participants will be performed on Day 1, the same day as study intervention intake.

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.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

1. treated with selexipag at the end of a parent study and:

   a) the parent study has established efficacy with a favorable benefit/risk profile for the indication under investigation

b) participant may continue to benefit from treatment with selexipag

c) has completed the EOT visit of the parent study

d) no alternative means of access to selexipag have been identified

2. women of childbearing potential must use an acceptable method of contraception throughout the study and until at least 1 month following the last dose of study intervention. Examples of methods of contraception allowed during the study are located in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

3. women of childbearing potential must have a negative urine (or serum if applicable) pregnancy test at screening on Day 1 or at the last visit of the parent study

4. must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

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

1. suspected or known pulmonary veno-occlusive disease (PVOD)

2. known allergies, hypersensitivity, or intolerance to selexipag or its excipients (Selexipag IB)

3. interruption of study intervention for more than 14 days since the last dose of study intervention taken in the parent study

4. female participant being pregnant, or breastfeeding, or planning to become pregnant at the time of screening and while enrolled in this study

5. uncontrolled thyroid disease

6. severe coronary heart disease or unstable angina, myocardial infarction within the last 6 months, decompensated cardiac failure if not under close medical supervision, severe arrhythmia, cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months, or congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH

7. known and documented severe hepatic impairment, eg, Child-Pugh Class C*

8. taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy, before the planned first dose of study intervention:

   - treatment with a strong CYP2C8 inhibitor (eg, gemfibrozil)
   - treatment with oral prostacyclin analogs (eg, beraprost, treprostinil) since the last dose of study intervention taken in the parent study
   - any investigational treatment other than selexipag

9. Criterion modified per Amendment 1

   9.1 plan to receive an investigational intervention (including investigational vaccines) other than selexipag.

*The assessment of hepatic impairment (Child-Pugh Score, Section 10.6, Appendix 6) must be fully documented for patients that have clinical signs and evidence (from central and/or local laboratory) of hepatic impairment.

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 the first dose of study intervention is given 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, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

The study intervention, selexipag, will be provided as tablets for oral administration.

The tablets are to be swallowed whole (ie, not crushed, split or chewed) with water, with or without food (tolerability may be improved when it is taken with food).

When enrolling in SOMBRERO, the participants will continue with the same individual maximum tolerated dose (iMTD) that they are taking at the end of their parent study, ie, same daily dose and same dosing frequency (bid or qd). Tablets will be available at all dose strengths, and participants will be instructed to take only one tablet of the required dose strength at each intake. Thus, the number of tablets per dose and tablet appearance in this study will differ from those used in the parent study depending on the iMTD (eg, if the iMTD in the parent study was 800 µg bid, participants took 4 × 200 µg tablets bid. After enrolling in SOMBRERO, they will take one 800 µg tablet bid). The color of the tablets will depend on the dose strength.

Description of Interventions

Study Intervention Name	Selexipag
Type	Drug
Dose Formulation	Round, film-coated tablets (all dose strengths). Differentiation of the tablets is based on the color and a debossing according to the selexipag dose in hundreds of µg (Selexipag IB).
Unit Dose Strength(s)	200, 400, 600, 800, 1,000, 1,200, 1,400 and 1,600 µg
Dosage Level(s)	The dose of selexipag administered at the end of the parent study will be maintained in the SOMBRERO study.
Route of Administration	Oral
Use	Investigational
Investigational Medicinal Product (IMP)	Selexipag
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Child-resistant packaging
	Each bottle will contain information and be labeled as required per country regulatory requirements.

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

Selexipag will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients (Selexipag IB).

For a definition of study intervention overdose, refer to Section 8.5, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored according to 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 to the participant, and the return of study intervention 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.

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.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants enrolled in the study. 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

Study Intervention Allocation

Randomization will not be used in this study.

Blinding

As this is an open study, blinding procedures are not applicable.

6.4. Study Intervention Compliance

Compliance with study intervention will be assessed at each visit by direct questioning. Compliance will be assessed at each on-site visit by counting returned tablets and documented in the source documents. Start and stop dates of study intervention, including dates for dose adjustments will also be recorded in the eCRF.

Participants will receive instructions on compliance with study intervention administration at the screening visit. 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

All concomitant therapies must be recorded in the eCRF throughout the study beginning with start of the first dose of study intervention through the EOS.

The use of the following concomitant therapies is allowed in the study:

- approved PH-specific therapies including PDE-5 inhibitors, endothelin receptor antagonists and/ or riociguat
- single administration of intravenous (IV) / inhaled prostacyclin or prostacyclin analogs used for acute vasodilator testing during a right-heart catheterization procedure
- temporary concomitant use of inhaled, IV, and subcutaneous (SC) prostacyclin and prostacyclin analogs (eg, epoprostenol, treprostinil, iloprost) is permitted, as deemed medically indicated by the investigator, to stabilize a participant with worsening of PH or to switch a participant to IV or SC treatment
- treatment with moderate inhibitors of CYP2C8 is allowed. If a moderate inhibitor of CYP2C8 (eg, clopidogrel, deferasirox, teriflunomide, levoflunomide) is started concomitantly with selexipag during the study, the dosing frequency of selexipag must be reduced to qd (resulting in halving of the daily dose). Dosing frequency of selexipag should be reverted to bid when co-administration of a moderate CYP2C8 inhibitor is stopped. If a participant is already receiving a moderate inhibitor of CYP2C8 at the time of study enrollment, the dose and dosing frequency of selexipag must be considered based on medical judgment at the time of study entry and when co-administration of a moderate CYP2C8 inhibitor is stopped.
- concomitant administration of rifampicin, an inducer of CYP2C8 and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, is allowed, but due to potential drug-drug interactions (ie, exposure to the active metabolite of selexipag reduced by half), dose adjustment of selexipag may be required. Concomitant administration of strong inhibitors of UGT1A3 and UGT2B7 (eg, valproic acid, probenecid, fluconazole) is allowed but caution is required since the interactions between UGT1A3 and/or UGT2B7 inhibitors and selexipag have not been studied, and a potential pharmacokinetic interaction cannot be excluded.

The use of the following therapies is prohibited in this study:

- other oral IP-receptor agonists (eg, treprostinil, beraprost) until study intervention discontinuation
- strong inhibitors of CYP2C8 (eg, gemfibrozil) until study intervention discontinuation
- any investigational treatment other than selexipag up to and including the EOS.

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

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).

The dose of selexipag can be adjusted at any time based on the judgment of the investigator.

If a participant needs to start treatment with a moderate CYP2C8 inhibitor at any time after entering the study, the dosing frequency of selexipag will be reduced to once daily (qd, in the morning). If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If the participant develops moderate hepatic impairment (Child-Pugh class B) once daily administration must be considered. If there is a study intervention interruption of 3 days or more, the participant will re-initiate the study intervention starting with 200 µg bid/qd (depending on the dosing frequency before interruption). If this dose is well tolerated, it will be up-titrated by the investigator in 200 µg increments using 200 µg tablets up to the iMTD of study intervention before treatment was interrupted, not exceeding a total daily dose of 3,200 µg (or 1,600 µg bid). During the up-titration period, the participant will receive 200 µg tablets corresponding to the dose strength level. When the iMTD is reached, the corresponding strength tablet will be administered. For each participant, the up-titration intervals will be determined according to the investigator's judgment.

In case of any tolerability issues or lack of efficacy, the dose of selexipag should be adjusted by the treating physician as necessary. For this purpose, the participant will down- or up-titrate the dose to the next possible dose using 200 µg tablets. Once a new and stable maintenance dose has been established based on acceptable tolerability, the participant should continue treatment with selexipag on this dose using 200 µg tablets until provided with respective tablets of the required dose strength.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- the participant withdraws consent to receive study intervention
- the investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- the female participant becomes pregnant. Refer to Section 10.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information.
- non-compliance with study intervention administration defined as study intervention interruption exceeding 14 consecutive days
- the participant initiates treatment with a strong CYP2C8 inhibitor (ie, gemfibrozil) or oral prostacyclin or prostacyclin analogs (eg, beraprost, treprostinil)
- there is a need for long-term use of inhaled, IV or SC prostacyclins or prostacyclin analogs (eg, epoprostenol, treprostinil, iloprost)
- the participant initiates any other investigational treatments
- the participant develops severe hepatic impairment (Child-Pugh class C) at any time during the study. If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If a participant has developed

severe hepatic impairment (Child-Pugh C) at any time during the study, the study intervention must be permanently discontinued.

- pulmonary edema due to pulmonary veno-occlusive disease (PVOD) occurs. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered. If confirmed the study intervention must be discontinued.

A participant who prematurely discontinues study intervention is not considered withdrawn from the study. A participant who prematurely discontinues study intervention and withdraws consent to participate in any further study assessments is considered as withdrawn from the study.

If a participant discontinues study intervention for any reason before EOS, then the EOT assessments should be obtained. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1.1. Temporary Discontinuation

If a participant is scheduled for an intervention that may temporarily prevent him/her from taking oral medications, selexipag treatment may be interrupted for not more than 14 days and the participant may temporarily switch to another IP receptor agonist medication with a different route of administration during that time. The participant will be allowed to restart selexipag once he/she can take oral medications again. When re-starting selexipag, it is recommended to begin with the lowest dose (ie, 1 tablet/200 µg bid) and to progressively increase the selexipag dose to reach the maximum dose that was previously tolerated by the participant. The decrease of the other IP receptor agonist dose will be done in parallel with the increase of the selexipag dose based on the participant's individual tolerability. If the participant experiences pharmacological side effects that cannot be tolerated while he/she is concomitantly taking selexipag and the other IP receptor agonist medication, a dose reduction or discontinuation of the other IP receptor agonist will be considered before considering a dose reduction or a discontinuation of selexipag.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- lost to follow-up
- withdrawal of consent
- death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal of Consent

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

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, attempts should be made 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). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA summarizes the frequency and timing of safety, and other measurements applicable to this study.

All study assessments are performed by qualified study personnel (medical, nursing or specialist technical personnel) and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional urine (or serum if applicable) pregnancy tests may be performed, 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 and:

- at monthly intervals (a urine pregnancy test will be performed at home by women of childbearing potential)

- at the end of study intervention (EOT, within 7 days of the last dose)
- 30 days after the last dose of study intervention (EOS).

To ensure proper pregnancy monitoring and contraception counseling, study site staff must call each woman of childbearing potential once per month to:

- remind the participant to perform a urine pregnancy test and
- collect the outcome of the urine pregnancy test.

During each study site visit or each TC, it must be verified whether the method of contraception used previously is still valid, in accordance with the protocol and correctly used by the participant.

The total blood volume to be collected is expected to be none or minimal. Urine pregnancy tests are allowed and serum pregnancy tests are not required but may be done if deemed necessary by the investigator.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Demographic data (age, sex, race, height, weight), PH etiology, WHO FC will be taken from the participant's parent study (or the double-blind core study preceding the parent study) and not recorded in the eCRF.

All AEs ongoing from the parent study at the time of enrollment in the SOMBRERO study will be recorded in the eCRF and will be considered as part of the participant's medical history.

The participant identifier from the parent study will be collected in the eCRF at enrollment in SOMBRERO (ie, Visit 1).

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- pharmacy manual / study site investigational product and procedures manual
- electronic data capture (eDC) manual
- Interactive Web Response System Manual
- sample ICF.

8.1. Safety Assessments

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the SoA:

– All AEs and special reporting situations, whether serious or non-serious, will be recorded in the eCRF.

– Pregnancies.

  A urine (or serum if applicable) pregnancy test for women of childbearing potential must be performed at screening if not already performed at the last visit of the parent study. Thereafter, urine pregnancy tests will be performed at home monthly, using the urine pregnancy test kits provided by the study site. A urine (or serum if applicable) pregnancy test will be performed at study site visits. The results of the pregnancy tests will not be recorded in the eCRF but must be kept in the source document. Pregnancies will be recorded on the AE page of the eCRF. Refer to Section 8.4 for further details on reporting of pregnancies.

Assessment of Child-Pugh score (as described in Section 10.6, Appendix 6), thyroid function, hemoglobin, vital signs may be performed for participants as clinically indicated. The results of these evaluations will not be recorded in the eCRF. In the event of clinical suspicion or manifestation of hyperthyroidism, thyroid function markers including thyroid stimulating hormone, free triiodothyronine (T3), and free thyroxine (T4) levels must be monitored by the investigator/delegate, and appropriate measures according to local clinical practice should be implemented.

For details on special reporting situations, refer to Section 10.4, Appendix 4.

8.2. Exploratory Assessment

8.2.1. Dose Reduction or Increase of Selexipag

Dose reduction or increase of selexipag and corresponding reason will be recorded in the eCRF.

8.3. Adverse Events and Serious Adverse Events

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.

For further details on AE and SAE reporting (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events

Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure (up to EOS for participants who enter a continued access program on the same day as the EOS Visit, see Section 4.1), which may include contact for follow-up of safety.

Serious Adverse Events

SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention (up to EOS for participants who enter a continued access program on the same day as the EOS Visit, see Section 4.1), must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All SAEs 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.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be sent to Sponsor.

8.3.2. 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 product quality complaint (PQC) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

All AEs and SAEs, including pregnancy with maternal exposure to selexipag, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

AE/SAEs still ongoing more than 30 days after study intervention discontinuation must be followed up until they are no longer considered clinically relevant or until stabilization. The follow--up information after the participant's EOS will not be collected by the Sponsor.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.4. After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study intervention.

8.4. Pregnancy

8.4.1. Reporting of Pregnancy

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

8.4.2. Follow-up of Pregnancy

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

Any AE associated with the pregnancy occurring during the follow-up period after study intervention discontinuation must be reported on separate AE pages in the eCRF. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported on an SAE form as described in Section 8.3.1.

8.5. Treatment of Overdose

For this study, overdose is defined by the intake of a dose > 1,600 µg or a total daily dose > 3,200 µg. For participants taking selexipag once daily (eg, moderate hepatic impairment or concomitant administration of a moderate CYP2C8 inhibitor), 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 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
- closely monitor the participant for (S)AEs and institute supportive measures as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein bound.
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

There will be no formal statistical hypotheses due to the design of this study. Only descriptive analyses will be performed.

9.2. Sample Size Determination

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

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All participants who take at least 1 dose of study intervention.

9.4. Statistical Analyses

9.4.1. Safety Endpoints

The primary safety endpoints are:

- frequency of AEs
- frequency of AEs leading to premature discontinuation of selexipag
- frequency of SAEs
- frequency of deaths
- number of pregnancies with maternal exposure to selexipag.

These safety endpoints will be assessed continuously from enrollment on Day 1 up to the EOS. See definition of AEs and SAEs in Section 10.4, Appendix 4.

9.4.2. Safety Analyses

Adverse Events

All safety analyses will be made on the Safety Population.

The verbatim terms used in the eCRF by investigators to identify AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE or SAE occurring at or after the initial administration of study intervention through the day of last dose plus 3 days is considered to be treatment-emergent (TEAEs). All reported TEAEs, and SAEs (up to 30 days after study intervention discontinuation) will be included in the analysis. For each event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings datasets, or participant narratives may be provided, as appropriate, for those participants who die, who prematurely discontinue study intervention due to a TEAE, or who experience an SAE. More specifically, descriptive summaries for all TEAEs, AEs leading to premature discontinuation of selexipag, SAEs (up to 30 days after study intervention discontinuation), and deaths using number of participants and percentage, as well as listing of pregnancies, will be provided.

9.4.3. Exploratory Endpoint and Analyses

The exploratory endpoint is the proportion of participants requiring selexipag dose reduction or increase by reason.

The proportion of participants requiring dose reduction or increase of selexipag will be summarized descriptively, by reason.

9.5. Interim Analysis

No formal interim analysis is planned. However, data from this study may be used for interactions with health authorities. Details about such analyses will be provided in the respective SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	adverse events
bid	twice daily
COVID-19	Coronavirus Disease 2019
CYP2C8	cytochrome $P_{450}2C8$
DTP	Direct-to-patient
eCRF	electronic case report form(s)
eDC	electronic data capture
EOS	End of Study
EOT	End of Treatment
FOIA	Freedom of Information Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
iMTD	individual maximum tolerated dose
INR	international normalized ratio
IP receptor	prostacyclin receptor
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
OL	open-label
PAH	pulmonary arterial hypertension
PDE-5	phosphodiesterase type 5
PH	pulmonary hypertension
PQC	product quality complaint
PTA	post-trial access
PVOD	pulmonary veno-occlusive disease
qd	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	free thyroxine
TC	telephone call
TEAE	treatment-emergent adverse event
UGT	uridine 5'-diphospho-glucuronosyltransferase
WHO FC	World Health Organization functional class

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local laboratory.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	Serum or Urine Pregnancy Testing (for women of childbearing potential only)

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 Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP 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 course of 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)
- IB (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 IB 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 (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where there is no intent to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

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

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) and contracts 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 for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatments, if needed. The physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

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

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.

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

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by 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.

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 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 an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

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

SOURCE DOCUMENTS

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

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

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

The following data will be recorded directly into the eCRF and will be considered source data:

- Parent study that the participant was enrolled in prior to enrolling in this study

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
- 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, pregnancy tests for women of childbearing potential) 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. This data is 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.

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

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition on Day 1 of this study, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events, for time of last AE recording).

Serious Adverse Event

A serious adverse event 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.

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. The expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

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
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention

- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- 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 the SAE Form.

PROCEDURES

Adverse Events

All AEs and special reporting situations, whether serious or non-serious must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the 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 open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, 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 after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a 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)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF): 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.
- The cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered an SAE.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

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, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

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

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding 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 and Collection of Pregnancy Information

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, Pregnancy and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential

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; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

permanently sterile
Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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 below.

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

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

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• Oral or injectable contraceptive agents, implants or transdermal contraceptive hormone[b]
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device
• Sterilization (bilateral tubal occlusion)
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• 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.)*
• Diaphragm; female condom or cervical cap; or partner's use of a condom, and any of these used in combination with a spermicide[c].
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Child-Pugh Classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to the following table (Adapted from (2012) Child-Pugh, FDA 2003):

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

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, five cycles per second waves.
• Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
• Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
• Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cycles per second delta activity.

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

10.7. Appendix 7: Guidance on Study Conduct During 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

Related to Protocol Section 8 - Study Assessments and Procedures

- 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.

Related to Protocol Section 8.1 - Safety Assessments and Section 10.2 - Clinical Laboratory Tests

- When participant visits to the study site are not possible, on-site pregnancy tests for women of childbearing potential will be performed at home for urine pregnancy tests or at a local laboratory if a serum pregnancy test is judged necessary by the study physician.

Related to protocol section 6.2 - 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 implemented where allowed per local regulations and if requested by the treating study physician. When Direct-to-patient (DTP) shipments are deemed necessary, the process should be coordinated between the site and the sponsor staff following the "COVID-19 DTP Guidance Document".

Related to protocol section 10.3 – Regulatory, Ethical and Study Oversight Considerations

- The sponsor may apply remote monitoring and/or remote auditing if on-site visits are not possible.
- Consenting and reconsenting of participants will be performed as applicable for the measures taken (including remote consenting by phone or video consultation) and according to local guidance for informed consent.

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 electronic case report form (eCRF).
- For serious adverse events (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.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. A summary of previous amendments is provided below.

Amendment 1, Version 2 (08 December 2020)

Overall Rationale for the Amendment: The overall reasons for this protocol amendment are to adapt safety reporting processes as part of the full transition of Actelion into Janssen, to align with TransCelerate Protocol Template, and to make minor corrections and editorial revisions.

Section Number and Name	Description of Change	Brief Rationale
Title Page	Legal name of the organization and confidentiality statement are updated.	To update administrative changes.
1.1. Synopsis-Objectives and endpoints; 3. Objectives and Endpoints; 9.4.1. Safety Endpoints	Primary objective is revised.	To clarify that continued treatment will be provided for participants who were previously enrolled in an Actelion-sponsored study with selexipag and who derived benefit from selexipag.
	A new primary endpoint is added as follows: '• **Frequency of adverse events (AEs)**' Consequently, the following endpoint "frequency of AEs related to dose changes or temporary interruption of selexipag" is no longer needed and is deleted.	Updated as all AEs whether serious or non-serious will be collected to align with Janssen's safety processes.
1.1. Synopsis-Number of participants; 9.2. Sample Size Determination	The maximum number of participants expected to roll-over from the GRIPHON OL study is revised to approximately 50 participants (earlier 114).	To update the number of participants based on the current information on the ongoing participants of GRIPHON OL study who will not have other options to access selexipag.
1.1. Synopsis-Intervention groups and duration; 6.5. Concomitant Therapy; 6.6. Dose Modification	Content related to dosing frequency of study intervention in presence of permitted moderate inhibitors of cytochrome P4502C8 (CYP2C8) is updated.	To clarify dosing adjustment with and without concomitant administration of moderate CYP2C8 inhibitor and under the circumstances of hepatic impairment.
1.1. Synopsis-Safety evaluations; 4.1. Overall Design; 8.1. Safety Assessments; 9.4.2. Safety Analyses	Statement related to safety evaluations is revised to include all AEs.	To align with Janssen's safety processes requiring the collection of all AEs.
1.3. Schedule of Activities (SoA)	SoA updated as all AEs are to be collected	
4.4. End of Study Definition	Content is revised to avoid duplication of information.	To delete the redundant information
5.2. Exclusion Criteria	Criterion 9 is revised as follows: 'plan to receive an investigational intervention (including investigational vaccines) **other than selexipag**.'	"Other than selexipag" added to avoid confusion.
5.3. Screen Failures	Screening failure-description (age at initial informed consent) has been removed.	Age at initial consent will not be used for participant identification for all study-related reports and communications

Section Number and Name	Description of Change	Brief Rationale
6.1. Study Intervention(s) Administered	Content of the section is revised.	To clarify that dose & dosing frequency of the study intervention at enrollment will be the same as in the parent study; to clarify that the color of the tablets will depend on the dose strength.
6.4. Study Intervention Compliance	Information about assessment of study intervention compliance is updated.	To provide proper information for assessment of study intervention compliance.
6.5. Concomitant Therapy;	Content revised as all concomitant therapies must be collected now.	To align with TransCelerate Protocol Template and processes that require collection of all concomitant therapies.
7.2. Participant Discontinuation/Withdrawal From the Study	Content related to use of locator agencies is deleted.	Not applicable to SOMBRERO and not provided as an option in the informed consent form (ICF).
8.1 Safety Assessments	Child-Pugh score assessment is included in safety assessments.	Added because this test will be needed for participants with known or suspected hepatic impairments.
8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events; 8.3.2. Follow-up of Adverse Events and Serious Adverse Events; 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Reference to AEs leading to premature discontinuation of study intervention (SI), related to dose changes or temporary interruption of SI has been removed from heading and content of the sections.	To align with Janssen's processes that require collection of all AEs whether serious or not.
8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events	Following content is updated. The initial and follow-up reports of a SAE should be ~~made by facsimile (fax)~~ **sent to Sponsor.**	
8.3.3. Regulatory Reporting Requirements for Serious Adverse Events	The list of disease related events not requiring expedited reporting is removed.	
8.3.4. After the 30-day follow-up period	A new section is included to provide information about reporting of serious adverse events (SAEs) occurring after 30-day follow-up period.	
8.4.1. Reporting of Pregnancy; 8.4.2. Follow-up of Pregnancy	Information about reporting and follow-up procedures for pregnancy is updated.	To reflect the standard Janssen wording and include monitoring of pregnant partners of male patients per Janssen safety reporting procedures.
8.5. Treatment of Overdose	Section of 'Treatment of Overdose' is updated to include definition of overdose and mandatory treatment provided by the investigator or treating physician in case of overdose.	Text updated to match changes with internal safety reporting processes.

Section Number and Name	Description of Change	Brief Rationale
9.2. Sample Size Determination	Following statement is added: '**It is foreseen that participants enrolled in other parent studies with selexipag may be enrolled in this study if they meet eligibility criteria**.'	To clarify about the possible enrolment of participants from other parent studies with selexipag if eligibility criteria are met.
9.3. Populations for Analysis Sets	Heading of the section is updated	To align with TransCelerate Protocol Template.
9.4.2. Safety Analyses	For analysis purpose, definition of maintenance dose is included.	To improve the clarity.
9.4.3. Exploratory Endpoints	The definition of baseline for WHO FC is clarified as the last WHO FC value assessed before the first dose of selexipag in the parent study **(or the double-blind core study preceding the parent study). Note: WHO FC is not collected in GRIPHON OL study, hence this endpoint is not applicable to participants from GRIPHON OL study.**	To avoid any confusion in the way baseline must be taken into account in the assessment of WHO FC changes over time
9.4.4.2. Overall Survival	The statement is revised as follow: 'Time to death will be calculated from the date of first intake of selexipag in the parent study **or the double-blind core study preceding the parent study**'.	To specify the date of first intake of selexipag to be taken into account in the calculation of "time to death" .
10.1. Appendix 1: Abbreviations	Terms 'COVID-19, 'DTP', 'FOIA' and 'INR' are included in the list of abbreviations.	To update new abbreviations.
10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Content related to 'Unlisted (Unexpected) Adverse Event/Reference Safety Information' is updated.	To align with TransCelerate Protocol Template.
10.7. Appendix 7: Child-Pugh Classification; 11. References	The Child-Pugh classification is included and the corresponding references are updated. Appendix 7 is cited throughout the protocol, wherever applicable.	To provide detailed information for the assessment of severity of liver diseases.
10.8. Appendix 8: Guidance on Study Conduct During Natural Disaster	Guidance on study conduct during the COVID-19 pandemic is added.	To describe measures to be taken to manage the study during the COVID-19 pandemic while access to sites is restricted
Throughout the protocol	• Term 'Study treatment' is replaced with 'Study intervention'. • Running footer updated. • Minor corrections and editorial revisions.	To maintain consistency throughout. To align with TransCelerate Protocol Template. To improve clarity of the content.

COVID-19 Appendix (27 November 2020)

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

11. REFERENCES

(2012 Child-Pugh) (2012) Child-Pugh. In: Vincent JL, Hall JB. (eds) Encyclopedia of Intensive Care Medicine. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-00418-6_3060.

(ClinicalTrials.gov) NCT03689244 A Study to Find Out if Selexipag is Effective and Safe in Patients With Chronic Thromboembolic Pulmonary Hypertension When the Disease is Inoperable or Persistent/Recurrent After Surgery (SELECT). https://clinicaltrials.gov/ct2/show/NCT03689244?term=SELECT&cond=CTEPH&draw=2&rank=1. Accessed 3 March 2020.

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

(FDA 2003) Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003. Available at : https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf [accessed 24 Aug 2020].

(Selexipag IB) Investigator's Brochure, JNJ-67896049 (selexipag), Edition 16 (02 Feb 2021) and Addendum to IB Edition 16 (25 May 2021). Actelion Pharmaceuticals Ltd .

(Sitbon 2015) Sitbon Q, Channick R, Chin KM, et al; GRIPHON Investigators. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2015 Dec 24;373(26):2522-2533.

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 Pharmaceutical Ltd and Janssen Research and Development, a Division of Janssen Pharmaceutica NV

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	26-Oct-2021 16:44:12 (GMT)	Document Approval
PPD	27-Oct-2021 07:43:59 (GMT)	Document Approval

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

Clinical Protocol

GUIDANCE ON STUDY CONDUCT DURING A NATURAL DISASTER /MAJOR DISRUPTION/PANDEMIC

Protocol Title

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

SOMBRERO

Protocol 67896049PUH3001; Phase 3b

JNJ-67896049/ACT-293987 (selexipag)

*Actelion Pharmaceuticals Ltd. ("Actelion") is a global organization that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

IND: 104504
EudraCT NUMBER: 2020-000475-21

Status:	Approved
Date:	19 May 2022
Prepared by:	Actelion Pharmaceutical Ltd and Janssen Research and Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-RIM-272313, 2.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL FOR IMPACTED COUNTRIES

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

STUDY CONDUCT DURING A NATURAL DISASTER/MAJOR DISRUPTION/PANDEMIC

GUIDANCE ON STUDY CONDUCT DURING NATURAL DISASTER/ MAJOR DISRUPTION/PANDEMIC

It is recognized that the natural disaster/major disruption/pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

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 travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed, if the situation allows.

If, as a result of the natural disaster/major disruption/pandemic, scheduled visits cannot be conducted in person at the study site, they 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 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 due to a natural disaster, a pandemic (eg, Coronavirus Disease 2019 [COVID-19]) or a major disruption should be clearly identified in the electronic Case Report Form (eCRF) by providing the specific prefix as instructed by the sponsor (eg, use the prefix "COVID-19-related if a participant discontinued due to COVID-19 pandemic").

NATURAL DISASTER/MAJOR DISRUPTION/PANDEMIC: 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. Modifications made to the study conduct as a result of a natural disaster, major disruption, or pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THE STUDY PROTOCOL 67896049PUH3001 DURING NATURAL DISASTER/MAJOR DISRUPTION/PANDEMIC

Scheduled Visits and Procedures (Protocol Section 1.3 & Section 8)

- 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.

Pregnancy tests (Protocol Section 8.1 & Section 10.2)

- When participant visits to the study site are not possible, on-site pregnancy tests for women of childbearing potential will be performed at home for urine pregnancy tests or where possible, at a local laboratory if a serum pregnancy test is judged necessary by the study physician.

Study Intervention (Protocol Section 6.2)

- 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 implemented where allowed per local regulations and if requested by the treating study physician.

Site Monitoring and Informed Consent (Protocol section 10.3)

- The sponsor may apply remote monitoring and/or remote auditing if on-site visits are not possible.
- Consenting on the specific temporary changes related to Natural disaster/Major disruption/Pandemic situations will be performed and documented according to local guidance for informed consent as applicable (Remote reconsenting of participants, eg, by phone or video consultation, may be considered according to local guidance).

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 serious adverse events (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.

INVESTIGATOR AGREEMENT

I have read this protocol appendix 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 Pharmaceutical Ltd and Janssen Research and Development, a division of Janssen Pharmaceutica NV

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	19-May-2022 10:29:26 (GMT)	Document Approval
PPD	19-May-2022 10:38:11 (GMT)	Document Approval