Selexipag / ACT-293987

Pulmonary arterial hypertension

Protocol AC-065A404

TRACE

A multi-center, double-blind, placebo-controlled, Phase 4 study in patients with pulmonary arterial hypertension to assess the effect of selexipag on daily life physical activity and patient's self-reported symptoms and their impacts

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Medical Emergency Hotline Toll phone number: [number]	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File

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CONTRACT RESEARCH ORGANIZATIONS INFORMATION

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A list of site-specific contact details for Contract Research Organizations (CROs) can be found in the Investigator Site File.

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Selexipag / ACT-293987

Indication

Pulmonary arterial hypertension

Protocol number, study acronym, study title

AC-065A404, TRACE: A multi-center, double-blind, placebo-controlled, Phase 4 study in patients with pulmonary arterial hypertension to assess the effect of selexipag on daily life physical activity and patient's self-reported symptoms and their impacts.

I approve the design of this study.

PPD

Title	Name	Date
Clinical Trial Physician	Maziar Assadi Gehr	5.12.18
Clinical Trial Statistician	Yoko Shiraga	5.12.18

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Selexipag / ACT-293987

Indication

Pulmonary arterial hypertension

Protocol number, study acronym, study title

AC-065A404, TRACE: A multi-center, double-blind, placebo-controlled, Phase 4 study in patients with pulmonary arterial hypertension to assess the effect of selexipag on daily life physical activity and patient's self-reported symptoms and their impacts.

I agree to the terms and conditions relating to this study as defined in this protocol, the Case Report Form (CRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the wellbeing of the patients).

I agree to conduct this study in accordance with the latest versions, respectively, of the Declaration of Helsinki principles (currently 2013 version), International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an independent ethics committee or institutional review board (IEC/IRB) prior to study start and signed informed consent from all patients included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the patients (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all patients or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual patient. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

	Country	Site number	Town	Date	Signature
Principal Investigator				_____	_____

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-Minute walk distance
6MWT	6-Minute walk test
AE	Adverse event
ANCOVA	Analysis Of Covariance
ATS	American Thoracic Society
b.i.d.	Twice daily
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTT	Clinical Trial Team
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DLPA	Daily life physical activity
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End-of-study
EOT	End-of-treatment
ePRO	Electronic Patient-Reported Outcome
ERA	Endothelin receptor antagonist
FAS	Full Analysis Set
FC	Functional class
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
HTD	Highest tolerated dose

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMD	Individualized maintenance dose
INN	International nonproprietary name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LVEDP	Left ventricular end diastolic pressure
mPAP	Mean pulmonary arterial pressure
MedDRA™	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal pro b-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PAH-SYMPACT®	Pulmonary Arterial Hypertension Symptoms and Impact
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PDE-5	Phosphodiesterase-5
PH	Pulmonary hypertension
PI	Principal Investigator
p.o.	Oral
PPS	Per-protocol Analysis Set
PRO	Patient-reported outcome
PVR	Pulmonary vascular resistance
QoL	Quality of Life
QS	Quality System
RHC	Right heart catheterization
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

SD	Standard deviation
sGC	Soluble guanylate cyclase
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TST	Total sleep time
USPI	United States Product Information
WASO	Wake after sleep onset
WHO	World Health Organization
WU	Wood Units

SUBSTANTIAL GLOBAL AMENDMENT 1

Amendment rationale

This amendment applies to global protocol AC-065A404, Version 1, dated 23 February 2017. The resulting amended global protocol is Version 2, dated 5 December 2018.

The reasons for this amendment are as follows:

Update of the dosing instructions for selexipag/placebo study drug, based on a recent drug-drug interaction study with a moderate CYP2C8 inhibitor, clopidogrel, as described in the Investigator Brochure version 13 of September 2018. In case of concomitant administration of a moderate inhibitor of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide) the dosing frequency of selexipag/placebo should be reduced to once daily and reverted to twice a day when co-administration of moderate CYP2C8 inhibitor is stopped.

Exclusion Criterion 12 of the TRACE protocol sets low-end thresholds for the values obtained from the pulmonary function test after the use of bronchodilator. If the values obtained without bronchodilator are above the threshold, they would not fall below the threshold in the presence of the bronchodilator. Therefore, the pulmonary function test can be performed in the presence or absence of bronchodilation whereby the eligible patient population remains unchanged.

The list of assessments has been modified without affecting endpoint variables. The sampling for blood biomarkers is not repeated at re-screening if the sampling has been performed at the initial screening, and there is no interaction with the Interactive Response Technology system at end of study.

Reference to the current Investigator Brochure Version 13, dated September 2018, is made as applicable.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document, showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The main sections of the protocol affected by this amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

Table 1 Study periods, visits at study site and assessments

PROTOCOL SYNOPSIS AC-065A404

TITLE	A multi-center, double-blind, placebo-controlled, Phase 4 study in patients with pulmonary arterial hypertension to assess the effect of selexipag on daily life physical activity and patient's self-reported symptoms and their impacts
ACRONYM	TRACE: EffecT of selexipag on daily life physical activity assessed by a weaRAble deviCE
OBJECTIVES	**Primary objective** • Evaluate the effect of selexipag on daily life physical activity (DLPA) of patients with pulmonary arterial hypertension (PAH). **Secondary objectives** • Evaluate the effect of selexipag on PAH symptoms and their impacts in patients' daily life. • Evaluate the effect of selexipag on exercise capacity, and disease severity in patients with PAH. • Evaluate the safety and tolerability of selexipag in patients with PAH. **Other objectives** • Explore potential association between traditional efficacy outcomes and DLPA. • Explore the levels and level changes of biomarkers potentially associated with PAH.
DESIGN	A prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, exploratory Phase 4 study.
PERIODS	**Screening period (duration up to 14 days):** The period includes the informed consent process and assessments determining patient eligibility at Visit 1. Some of the assessments provide baseline data. At Visit 1 the devices for the assessment of DLPA and PAH-SYMPACT® are given to the patient for outpatient use. Visit 2 defined as Day 1 is being scheduled. **Baseline period (duration 14–28 days):** The period starts at the end of Visit 1 and ends with randomization at Visit 2 on Day 1. The actigraphy device is worn for the entire period,

	24 hours per day (except during charging) for the collection of baseline DLPA. The recording of DLPA starts on the day of Visit 1. The PAH-SYMPACT® is assessed daily over a period of 7 days starting on Day −14. The start of the PAH-SYMPACT® can be delayed until Day −11, if the start on Day −14 has been missed. Valid baseline data for DLPA and PAH-SYMPACT® are required for eligibility. **Treatment period (duration 24 weeks):** For eligible patients with valid baseline data for DLPA and PAH-SYMPACT®, the period starts on Day 1 (Visit 2) with confirmation of eligibility and randomization to one of the two double-blind treatment arms. Patients will receive the first dose of study treatment on Day 1. From Day 1 up to end of Week 12 (Day 85) study treatment will be titrated to the highest individually tolerated dose. Patients will be called weekly by the site staff to guide the titration process, assess safety/tolerability, and support compliance with the actigraphy device. From Week 13 to Week 24 the individualized highest tolerated dose (HTD) is intended to be maintained (individualized maintenance dose [IMD]). Change of study treatment dose is allowed if needed for efficacy or tolerability reasons. Patients will continue to wear the actigraphy device during the whole 24-week period. At Week 15 and Week 23, PAH-SYMPACT® is assessed by the patient at their actual location (home, vacation, etc.). Patients will be called by the site staff on the first day of each PAH-SYMPACT® assessment period (Week 15 and Week 23) and at Week 20, to assess safety/tolerability, and to support compliance with the actigraphy device and the PAH-SYMPACT®. Visits at the study site are scheduled on Day 1 (Visit 2), Week 16/Day 113 (Visit 3), and Week 24/Day 169 (Visit 4). An unscheduled visit is required for study treatment dispensing if dose is increased after Visit 3. At Visit 4, study treatment is terminated (end-of-treatment, EOT). Upon premature discontinuation of study treatment prior to Week 24, the Visit 4 assessments should be performed within 10 days. Patient and investigator remain blinded regarding study treatment. **Post-treatment safety follow-up period (duration 30 days):** This period starts 1 day after EOT, defined as the last day of

	intake of study drug. Patients will be followed by telephone regarding ongoing and new adverse events (AEs) at investigator's discretion. The period is completed by an end-of-study (EOS) telephone call 30 days after EOT. This telephone call represents the end of the patient's study participation. At any time during the study, unscheduled telephone calls or visits at the study site may be conducted if medically indicated at the discretion of the investigator.
PLANNED DURATION	Approximately 20 months from first patient, first visit to last patient, last visit.
SITE(S) / COUNTRY(IES)	The study will be conducted at approximately 45 sites in approximately 12 countries.
SUBJECTS / GROUPS	Approximately 100 patients will be randomized in a 1:1 ratio to the two treatment groups (approximately 50 patients per group), stratified by region (Europe/rest of the world versus North America).
INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any study mandated procedure. 2. Male and female patients with symptomatic PAH, aged from 18 years to 75 years inclusive. A woman of childbearing potential [see definition in Section 4.5.1] is eligible only if the following applies: a) Negative serum pregnancy test at Screening Visit 1 and a negative urine pregnancy test at randomization, AND b) Agreement to undertake monthly urine pregnancy tests during the study up to 30 days after study treatment discontinuation AND c) Agreement to use an acceptable method of contraception [see definition in Section 4.5.2] from screening to 30 days after study treatment discontinuation. 3. Diagnosis of PAH belonging to one of the following subgroups of Group 1 pulmonary hypertension (PH) according to the updated clinical classification [Galiè 2015a]:

	1.1. Idiopathic (IPAH) 1.2. Heritable (HPAH) 1.3. Drugs or toxins induced 1.4. Associated (APAH) with one of the following: 1.4.1. Connective tissue disease 1.4.2. Human immunodeficiency virus (HIV) infection 1.4.4. Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) ≥ 1 year after surgical repair. 4. Documented hemodynamic diagnosis of PAH by right heart catheterization (RHC). Prior to randomization the most recently performed RHC at rest showing: a) Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg; and b) Resting pulmonary vascular resistance (PVR) ≥ 240 dyn•s•cm^{-5} or 3 Wood Units; and c) Pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg. 5. Treatment with an endothelin receptor antagonist (ERA) for at least 90 days and on a stable dose for 30 days prior to randomization. 6. Possible treatment with a phosphodiesterase-5 (PDE-5) inhibitor or soluble guanylate cyclase (sGC) stimulator must be ongoing for at least 90 days and on a stable dose for 30 days prior to randomization. 7. WHO functional class (FC) II or III at randomization. 8. 6-minute walk distance (6MWD) ≥ 100 m at Visit 1. 9. Ability to walk without a walking aid. 10. Valid baseline data at Visit 2 for DLPA and PAH-SYMPACT® defined as: a) DLPA: Within the last 14 days (excluding Day 1), at least 9 days each with a minimum of 14 hours wear time; b) PAH-SYMPACT®: Of the 7-day PAH-SYMPACT®

	assessment period, 5 days with complete data of the symptom part and 1 day with complete data of the impact part.
EXCLUSION CRITERIA	1. PH Groups 2–5 according to the updated clinical classification [Galiè 2015a], and PAH Group 1 subgroups that are not covered by the inclusion criterion 3. 2. Patients on a PAH-specific **monotherapy** targeting the nitric oxide pathway (i.e., PDE-5 inhibitor or sGC stimulator). 3. Patients treated with prostacyclin, prostacyclin analog, or prostacyclin receptor agonist) at any time prior to Day 1 (administration for vasoreactivity testing is permitted; previous prostacyclin / prostacyclin analogs used intermittently for the treatment of digital ulcers or Raynaud's phenomenon are permitted if stopped > 6 months prior to Day 1). 4. Any hospitalization during the last 30 days prior to Visit 1. 5. Worsening in WHO FC during the last 30 days prior to Visit 1. 6. Severe coronary heart disease or unstable angina. 7. Myocardial infarction within the last 6 months. 8. Decompensated cardiac failure. 9. Ongoing severe arrhythmias. 10. Cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months. 11. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH. 12. Presence of one or more of the following signs of relevant lung disease at the last examination any time up to Visit 1: a) Diffusing capacity of the lung for carbon monoxide < 40% of predicted UNLESS computed tomography

	reveals no or mild parenchymal lung disease; OR b) Forced vital capacity < 60% of predicted[1]; OR c) Forced expiratory volume in one second < 60% of predicted[1]. 13. Documented severe hepatic impairment (with or without cirrhosis) at Visit 1, defined as Child-Pugh Class C. 14. Documented severe renal insufficiency at Visit 1, defined as estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL. 15. Hemoglobin < 80 g/L (< 4.96 mmol/L) at Visit 1. 16. Known or suspected uncontrolled hyperthyroidism. 17. Known or suspected pulmonary veno-occlusive disease. 18. Ongoing or planned dialysis. 19. Body mass index above 40 kg/m^2 at Visit 1. 20. Sitting systolic blood pressure below 90 mmHg at Visit 1. 21. Treatment with a strong inhibitor of CYP2C8 (e.g., gemfibrozil). 22. Receiving or having received any investigational drugs within 90 days prior to Visit 1. 23. Participation in a cardio-pulmonary rehabilitation program based on exercise training within 8 weeks prior to Visit 1. Such program must not be started during the course of the study. 24. Concomitant life-threatening disease with a life expectancy of less than 12 months. 25. Known hypersensitivity to any of the excipients of the study treatment formulation. 26. Pregnancy, breastfeeding, or intention to become pregnant during the study. 27. Any factor or condition likely to impair adherence to

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

	protocol mandated procedures, as judged by the investigator.
STUDY TREATMENTS	**Investigational treatment** Selexipag (ACT-293987) 200 mcg oral tablet twice daily (b.i.d.). **Comparative treatment** Matching placebo 200 mcg oral tablet b.i.d. Study treatments will be provided as film-coated tablets in childproof bottles of 120 tablets. Store below 25 °C (77 °F). Keep the bottle tightly closed in order to protect from moisture. **Individualized dose titration (Weeks 1 to 12)** Each patient should be titrated to the individualized HTD, which can range from 200 mcg b.i.d. to 1600 mcg b.i.d. The starting dose is 200 mcg b.i.d., approximately 12 hours apart. The dose is increased in increments of 200 mcg b.i.d., usually at weekly intervals. At the beginning of treatment and at each up-titration step it is recommended to take the first dose in the evening. During dose titration some adverse reactions, reflecting the mode of action of the study treatment (such as headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing), may occur. They are usually transient or manageable with symptomatic treatment. However, if a patient reaches a dose that cannot be tolerated or managed, the dose should be reduced to the previous dose level. In patients in whom up-titration was limited by reasons other than adverse reactions reflecting the mode of action of study treatment, a second attempt to continue up-titration to the HTD up to a maximum dose of 1600 mcg b.i.d. may be considered until Week 12. **Individualized maintenance dose (Weeks 13 to 24)** The individualized maintenance dose is the HTD reached during individualized dose titration and should be maintained from Week 13 to Week 24. Change of study treatment dose is allowed if needed for efficacy or safety/tolerability reasons. If the therapy over time is less tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next

	lower dose should be considered. The dose may be increased (to a maximum dose of 1600 mcg b.i.d.) if the patient may benefit from a higher dose, as judged by the investigator.
ENDPOINTS	**Primary endpoints** • Change from baseline to Week 24/EOT in actigraphy-assessed DLPA as measured by: o Daily time spent (minutes) in non-sedentary activity (> 100 activity counts per minute) o Percentage of daily time spent in non-sedentary activity (> 100 activity counts per minute) o Total DLPA in counts/min o Sleep: Total sleep time; minutes, wake after sleep onset; minutes, number of awakenings, efficiency (percentage) The study is designed as exploratory, and therefore all actigraphy variables are listed under primary endpoints. **Secondary endpoints** • Change from baseline to Week 24/EOT for following PAH-SYMPACT® domain scores: o Cardiovascular symptom domain score o Cardiopulmonary symptom domain score o Physical impact domain score o Cognitive/emotional impact domain score • Change from baseline to Week 24/EOT for following variables: o WHO FC o 6MWD o Borg dyspnea index at 6MWT o N-terminal pro b-type natriuretic peptide (NT-proBNP) **Other endpoints** • Change from baseline to Week 24/EOT for blood biomarkers associated with, e.g., PAH worsening, right/left ventricle function, inflammation. • Association between actigraphy variables and other efficacy endpoints (PAH-SYMPACT®, 6MWD, etc.) **Safety endpoints** • Treatment-emergent AEs and serious AEs up to 30 days

	after study treatment discontinuation. • AEs leading to discontinuation of study treatment. • Change from baseline in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points during the study. • Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	All statistical analyses will be conducted by Actelion or by designated CRO supervised by Actelion. A Statistical Analysis Plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations. Analysis sets: The Screened Analysis Set includes all patients who are screened and have a patient identification number. The Full Analysis Set (FAS) includes all patients randomly assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible: • Patients are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received), • All available data are included. The Per-protocol Analysis Set comprises all patients who received study treatment and who complied with the protocol sufficiently to allow assessment of the treatment effects. Criteria for sufficient compliance include exposure to treatment, availability of measurements and absence of major protocol deviations that have an impact on the treatment effect. The full list of criteria will be detailed in the SAP before making the full randomization information available. The Safety Set includes all patients who received at least one dose of study treatment, and the analysis will be based on the actual treatment received. Primary analysis: This study is designed as exploratory with the purpose to generate hypotheses on new endpoints. All analyses performed will be descriptive in nature with summary statistics and

	associated 95% confidence intervals (CI) provided when applicable. Any p-value provided as result of a statistical model is to be considered as exploratory only. No adjustment for multiplicity will be performed. There will be no interim analysis. All actigraphy variables will be summarized by period of 14 days: Baseline (last 14 days before first dose), Week 2 (Day 1–14), Week 4 (Day 15–28), and so on until Week 24 (Day 155–168) or EOT (last 14 days period on study treatment) in case of premature discontinuation. Any actigraphy data recorded after Day 168/EOT will not be considered in summary statistics and will be listed only. For all actigraphy variables (continuous), change from baseline to Week 24/EOT will be analyzed (on the FAS) using an analysis of covariance including terms for treatment and region, and baseline values as covariates. The differences in least square means between treatment and placebo, corresponding 2-sided 95% CI and p-value will be provided. All actigraphy variables will be also reported overtime with actual values, absolute change and percentage change from baseline at each time point (14 days periods). Daily time spent and percentage of daily time spent will be also displayed according to activity categories "sedentary", "light", "moderate", "vigorous" and "very vigorous" based on the Freedson Adult algorithm [Freedson 1998]. <u>Secondary/exploratory analyses</u>: PAH-SYMPACT® domain scores and others PAH-related variables (6MWD, Borg dyspnea index, NT-proBNP) will be analyzed similarly as actigraphy variables (as continuous). WHO FCs will be described by shift tables from baseline to each time point. The association between actigraphy variables and others efficacy endpoints (PAH-SYMPACT® domain scores, 6MWD, NT-proBNP) will be described using correlations, scatter plots and regressions. Details will be provided in the SAP. <u>Safety analysis:</u> All safety analyses will be performed on the Safety Set using

	descriptive statistics. <u>Sample size:</u> There are no longitudinal data available for actigraphy variables in PAH patients. Therefore, the study is designed as exploratory and sample size is based on enrolment capabilities: 100 patients will be randomized in total (50 in placebo group and 50 in selexipag group).
STUDY COMMITTEES	A Steering Committee has been appointed by Actelion to contribute to the design of the protocol, the oversight of study conduct, the evaluation of results, and the support in publication. The committee is governed by a Steering Committee charter.

Table 1 Study periods, visits at study site and assessments

Telephone calls from the study site to the patient and assessments during telephone calls are shown in Table 2.

PERIOD (DURATION)		SCREENING (up to 14 days)	BASELINE (at least 14 days)	TREATMENT (24 weeks)						FOLLOW-UP (30 days)
VISIT	Number	1		2		3		4	*U1, U2, …*	P16
	Name	Screening	Actigraphy, ePRO period	Randomization[1]	ePRO period	Intermediate visit	ePRO period	End-of-treatment	*Unscheduled visits*[3]	End-of-study telephone call
	Time (Time window)	Days −28 to −15	Days −14 to −1	Day 1	Week 15 Days 99 to 105 (+3 days)	Week 16 Day 113 (−4 to +7 days)	Week 23 Days 155 to 161 (+3 days)	Week 24[2] Day 169 (−4 to +14 days)	*Any day between Day 1 and EOT+30 days*	End-of-Treatment +30 days (+10 days)
Informed consent[4]		X								
IRT interaction		X		X		X		X	*X*[11]	
Eligibility		X		X						
Demographics, PAH		X								
Medical history		X								
Prev./conc. therapies		X		X[5]		X[5]		X[5]	*X*[5]	X[5]
Vital signs (BP, HR, body weight, height[6])		X		X		X		X	*X*	
WHO FC		X		X		X		X	*X*	
6MWT/Borg index		X				X		X	*X*	
NT-proBNP, biomarkers		X[13]				X		X	*X*	
Hematology, chemistry		X						X	*X*	
Contraceptive methods used, pregnancy test[7, 8]		X		X		X		X	*X*	X
Actigraphy[9]			Every day, 24 hours per day							
PAH-SYMPACT®[10]			X		X		X			
Study treatment dose				X		X[5]		X[5]	*X*[5, 11]	
Study treatment dispensing/return				X		X		X	*X*[11]	
AE and SAE[12]		X		X		X		X	*X*	X

1) All assessments are to be done prior to first intake of study drug.
2) In case of premature study treatment discontinuation, this visit with all assessments should be performed within 10 days after end-of-treatment, if possible.
3) Unscheduled visits may be performed at any time during the study and may include all, some or additional assessments, based on the judgment of the investigator. Study assessments must be entered in the eCRF.
4) Prior to any study mandated assessments.
5) Only the changes are recorded.
6) Height is measured at Visit 1 only.
7) Serum pregnancy tests performed by central laboratory at Visit 1, Visit 3 (Week 16) and Visit 4 (Week 24).
8) Urine pregnancy tests performed at study site during Visit 2 and by patient at home within 3 days prior to the telephone call at EOT + 30 days.
9) Actigraphy data are collected starting at Visit 1, uploaded by patients daily, AND by the site at all site visits.
10) The PAH-SYMPACT® questionnaire is being completed daily during each of the 3 7-day ePRO periods starting on Day −14, Day 99 (Week 15), and Day 155 (Week 23).
11) An unscheduled visit is required for study treatment dispensing if dose is increased after Visit 3.
12) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after EOT must be recorded in the eCRF. SAEs must be reported to Actelion drug safety on an SAE form.
13) No sampling for blood biomarkers at re-screening, if collected at initial screening.

6MWT, 6-minute walk test; AE, adverse event; BP, blood pressure; eCRF, electronic Case Report Form; EOT, end-of-treatment; ePRO, electronic patient-reported outcome; HR, heart rate; IRT, interactive response technology; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PAH-SYMPACT®, Pulmonary Arterial Hypertension Symptoms and Impact questionnaire; SAE, serious adverse event; WHO FC, World Health Organization functional class.

Table 2 Telephone calls from the study site to the patient, and assessments

PERIODS (DURATION)		TREATMENT (24 weeks) Weeks 1 to 12	TREATMENT (24 weeks) Weeks 13 to 24			*Any time*	FOLLOW-UP (30 days)
Telephone call	**Number**	**P1 to P12**	**P13**	**P14**	**P15**	***UP1, UP2, …***	**P16**
	Name	**Weekly telephone calls**	**Week 15**	**Week 20**	**Week 23**	***Unscheduled telephone call[2]***	**End-of-study telephone call**
	Time (Time window)	**Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85 (±3 days)**	**99 (+3 days)**	**141 (±3 days)**	**155 (+3 days)**	***Any day between Day 1 and EOT+30 days***	**End-of-treatment +30 days (+10 days)**
Conc. therapies[3]		X	X	X	X	*X*	X
Contraceptive methods used[3], urine pregnancy test[4]		Days 29, 57, 85		X			X
PAH-SYMPACT®[1]			X		X		
Study treatment dose[3]		X	X	X	X	*X*	
AE and SAE[5]		X	X	X	X	*X*	X

1) PAH-SYMPACT® refers to reminding the patient of the start of the PAH-SYMPACT® assessment period. The call cannot be made earlier than the day indicated but can be postponed by a maximum of 3 days.
2) Unscheduled telephone calls may be performed at any time during the study and may include all, some or additional assessments, based on the judgment of the investigator. Study assessments must be entered in the eCRF.
3) Only the changes are recorded.
4) Urine pregnancy tests are performed by patient at home within 3 days prior to the telephone calls.
5) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after EOT must be recorded in the eCRF. SAEs must be reported to Actelion drug safety on an SAE form.

AE, adverse event; eCRF, electronic Case Report Form; EOT, end-of-treatment; PAH-SYMPACT®, Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire; SAE, serious adverse event.

PROTOCOL

1 BACKGROUND

1.1 Indication

Pulmonary arterial hypertension (PAH) is a serious chronic disorder of the pulmonary circulation of diverse etiology and pathogenesis. PAH is characterized by a progressive increase in pulmonary artery pressure (PAP) and in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death [Benza 2010, Kylhammar 2014, Oudiz 2013]. The complex pathogenesis of PAH involves dysfunction of three key pathways: the endothelin pathway, the nitric oxide pathway, and the prostacyclin pathway [Humbert 2004].

PAH is hemodynamically defined as a resting mean pulmonary artery pressure (mPAP) of at least 25 mmHg with normal pulmonary artery wedge pressure (PAWP) (or left ventricular end diastolic pressure [LVEDP]) of 15 mmHg or less, and a PVR greater than 3 Wood Units (WU) [Hoeper 2013].

The updated clinical classification of pulmonary hypertension (PH) [Galiè 2015a] classifies the numerous conditions that are known to lead or be associated with the development of PAH into 4 groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause (idiopathic), in a familial setting (heritable), as the result of the use of certain drugs and toxins, or it can be associated with a connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.

1.2 Study treatment

Uptravi® (Selexipag) has been approved in the US and Europe for the indication of long-term treatment of PAH. More detailed information on selexipag can be found in the Investigator's Brochure (IB) [Selexipag IB]

1.2.1 Nonclinical results

Selexipag is an orally available non-prostanoid prostacyclin receptor agonist. Whilst active by itself, selexipag is hydrolyzed to an active metabolite with prolonged terminal half-life and a high selectivity for the prostacyclin receptor. Selexipag and its metabolite possess anti-fibrotic, anti-proliferative, and anti-thrombotic activity. Oral selexipag is effective in an animal model of PAH, improving hemodynamic and structural factors leading to increased survival.

1.2.2 Clinical pharmacology

For interactions as well as the pharmacodynamics and pharmacokinetics of selexipag, see the IB [Selexipag IB].

1.2.3 Clinical efficacy

In the multicenter, double-blind, placebo-controlled, event-driven, Phase 3 clinical trial GRIPHON, conducted in 1156 patients with PAH, selexipag demonstrated a clinically and statistically significant 40% risk reduction compared to placebo in the occurrence of a first morbidity/mortality event up to end-of-treatment (EOT) (log-rank $P < 0.0001$) [Sitbon 2015]. Results of all supportive analyses on the primary endpoint were consistent with that of the main analysis, and the observed treatment effect was also consistent across subgroups (PAH etiology, region, ethnicity, gender, age, WHO functional class [FC], and baseline PAH background medication).

The secondary endpoints of change from baseline to Week 26 in 6MWD measured at trough, and of time to first PAH-related death or hospitalization due to PAH, showed a statistically significant effect favoring selexipag over placebo. The secondary endpoints of absence of worsening in WHO FC from baseline to Week 26 and of time to death of all causes up to study closure did not show a difference between selexipag and placebo [Sitbon 2015].

1.2.4 Summary of safety profile

In the GRIPHON trial, patients were treated for up to 4.2 years. The most frequently reported adverse events (AEs) in the selexipag group were those associated with prostacyclin treatment: headache (65% vs 32% in placebo group), diarrhea (42% vs 18%), nausea (33% vs 18%), jaw pain (26% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), and myalgia (16% vs 6%). A total of 43.8% and 47.1% of patients in the selexipag and placebo groups, respectively, had at least 1 serious adverse event (SAE). The great majority of SAEs were consistent with the underlying PAH condition. PAH worsening and right ventricular failure were the most frequently reported SAEs, and both were reported at lower frequencies in the selexipag group (14.4% and 5.9%, respectively) compared to the placebo group (22.0% and 7.1%, respectively). A total of 31.7% of patients in the selexipag group and 37.1% in the placebo group had at least one AE leading to discontinuation of study treatment. Other than prostacyclin-associated AEs, most of the AEs that led to discontinuation of study treatment were SAEs associated with underlying PAH disease.

Overall, in the GRIPHON study, the nature and incidence of typical prostacyclin-associated AEs (i.e., headache, flushing, diarrhea, nausea, vomiting, jaw pain, myalgia and arthralgia) on selexipag was largely in line with that observed with prostacyclin and prostacyclin analogs [Sitbon 2015].

Hypotension was reported more frequently in the selexipag group compared to the placebo group (5.9% and 3.8%, respectively). In the selexipag group, 9.7% of patients had systolic blood pressure (SBP) < 90 mmHg on at least one occasion, compared to 6.7% in the placebo group. A decrease from baseline of > 40 mmHg in SBP was reported for 2.3% and 3.0% of patients in selexipag and placebo groups, respectively.

Bleeding was not observed more frequently in selexipag-treated patients compared to placebo, including in those patients treated concomitantly with anticoagulants. Anemia was reported more frequently in the selexipag group and a small reduction in hemoglobin was observed at most post-baseline visits.

Hyperthyroidism was reported more frequently in the selexipag group compared to the placebo group. Corresponding laboratory changes were a small reduction in thyroid-stimulating hormone at most post-baseline visits. A possible association between thyroid disorders and PAH is described in the literature [reviewed in Marvisi 2013]. Previously published investigations showed that prostaglandins may influence thyroid function by a direct effect on specific prostaglandin membrane receptors [Chadha 2009].

1.3 Purpose and rationale of the study

Patient-centered outcomes are outcomes from medical care that are important to patients. Insurance payments are increasingly linked to the provision of patient-centered outcomes. New measures are necessary for measuring treatment effect in a real life, day-to-day setting. It is also recognized that no single measurement will adequately capture the aspects of disease and treatment from the point of view of and relevant to the patient. Such patient-centered outcomes may play an important role in patient follow-up and treatment reimbursement in the future.

Actigraphy is a non-invasive method for the collection of information about the physical activity of patients in their real-life, day-to-day setting [Godfrey 2008]. The technology can be used for capturing objective information on sleep/wake behavior, circadian rhythm, and physical activity. Devices validated for the use in clinical trials are available and allow for monitoring the adherence to proper wearing and handling. Actigraphy can provide insights into the effect of an investigational therapy on the patient's activity and mobility by comparing patient's baseline activity and sleep behavior to their changes after the intervention. This allows assessing whether the treatment has a positive impact on the exercise capacity of the patient. In contrast to other methods for assessing the exercise capacity of the patient (i.e., 6-minute walk test [6MWT]) actigraphy allows this assessment to be performed in the every-day environment of the patient [Mainguy 2011, Okumus 2016, Pugh 2012, Ulrich 2012].

Patient-reported outcome (PRO) is a method by which the patient's perceptions and experiences are collected by using a questionnaire. The most widely used PRO for

evaluating symptoms, functioning and quality of life (QoL) in PAH clinical studies is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [McKenna 2006]. In addition, other non-PAH specific QoL questionnaires have been used previously in PAH studies. However, as these questionnaires were not developed specifically for use in PAH, they may not capture the aspects most important to patients with PAH and would not meet the FDA guidance requirements for a validated questionnaire [FDA 2009]. PAH-SYMPACT® is a PAH specific PRO tool developed according to the FDA guidelines that allows the assessment of PAH-specific SYMptoms and their physical and cognitive/emotional impact [McCollister 2016].

The assessments of daily life physical activity (DLPA) and PAH-SYMPACT® in a Phase 4 clinical study with selexipag will provide patient-centered, real-world, and PAH-specific information about the effects of selexipag on the daily life of patients with PAH. The additional assessment of objective clinical variables (i.e., WHO FC, 6-minute walk distance [6MWD]) may reveal their potential correlation with the patient's daily life experience and shed new light on disease mechanism.

1.4 Summary of known and potential risks and benefits

The study mandated procedures at site visits (i.e., blood draw, 6MWT) and wearing the actigraphy device during the participation in the study do not pose a risk to the study participants. Given the extensive and long-term controlled efficacy and safety data available with selexipag [see Section 1.2] and the careful follow-up of patients mandated by this protocol (i.e., clinical examination, laboratory checks, weekly telephone calls during the titration phase of study treatment), the benefit/risk assessment supports the treatment of the patients with selexipag for the purpose of the current study.

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

2 STUDY OBJECTIVES

2.1 Primary objective

To evaluate the effect of selexipag on DLPA of patients with PAH.

2.2 Secondary objectives

- To evaluate the effect of selexipag on PAH symptoms and the impact on patients' daily life.
- To evaluate the effect of selexipag on exercise capacity and disease severity in patients with PAH.

- To evaluate the safety and tolerability of selexipag in patients with PAH.

2.3 Other objectives

- Explore potential association between traditional efficacy outcomes and DLPA.
- Explore the levels and level changes of biomarkers potentially associated with PAH.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, exploratory Phase 4 study.

Approximately 100 patients will be randomized in a 1:1 ratio to either selexipag or placebo. Treatment allocation will be stratified by region, i.e., Europe/rest of the world vs North America.

The study will be conducted in approximately 45 sites in approximately 12 countries. Randomization will proceed until the required number of subjects has been reached. It will be competitive across participating sites. Actelion may replace sites with no subject enrollment.

3.1.1 Study periods

The study comprises the following consecutive periods:

Screening period (duration up to 14 days): The period includes the informed consent process and assessments determining patient eligibility at Visit 1. Some of the assessments provide baseline data. At Visit 1 the devices for the assessment of DLPA and PAH-SYMPACT® are given to the patient for outpatient use. Visit 2 defined as Day 1 is being scheduled.

Baseline period (duration at least 14 days, at most 28 days): The period starts at the end of Visit 1 and ends with randomization at Visit 2 on Day 1. The actigraphy device is worn for the entire period, 24 hours per day (except during charging) for the collection of baseline DLPA. The recording of DLPA starts on the day of Visit 1. The PAH-SYMPACT® is assessed daily over a period of 7 days starting on Day −14. The start of the PAH-SYMPACT® can be delayed until Day −11, if the start on Day −14 has been missed. Valid baseline data for DLPA and PAH-SYMPACT® are required for eligibility.

Treatment period (duration 24 weeks): For eligible patients with valid baseline data for DLPA and PAH-SYMPACT®, the period starts on Day 1 (Visit 2) with confirmation of eligibility and randomization to one of the two double-blind treatment arms. Patients will receive the first dose of study treatment on Day 1. From Day 1 up to end of Week 12

(Day 85) study treatment will be titrated to the highest individually tolerated dose. Patients will be called weekly by the site staff to guide the titration process, assess safety/tolerability, and support compliance with the actigraphy device. From Week 13 to Week 24 the individualized highest tolerated dose (HTD) is intended to be maintained (individualized maintenance dose [IMD]). Change of study treatment dose is allowed if needed for efficacy or tolerability reasons. An unscheduled visit is required for study treatment dispensing if dose is increased after Visit 3 (Week 16).

Patients will continue to wear the actigraphy device during the whole 24-week period. At Week 15 and Week 23, PAH-SYMPACT® is assessed by the patient at their actual location (home, vacation, etc.). Patients will be called by the site staff on the first day of each PAH-SYMPACT® assessment period (Day 99 for Week 15 and Day 155 for Week 23) and at Week 20, to assess safety/tolerability, and to support compliance with the actigraphy device and the PAH-SYMPACT®. Visits at the study site are scheduled on Day 1 (Visit 2), Week 16/Day 113 (Visit 3), and Week 24/Day 169 (Visit 4). At Visit 4, study treatment is terminated (EOT). Upon premature discontinuation of study treatment prior to Week 24, the Visit 4 assessments should be performed within 10 days. Patient and investigator remain blinded regarding study treatment.

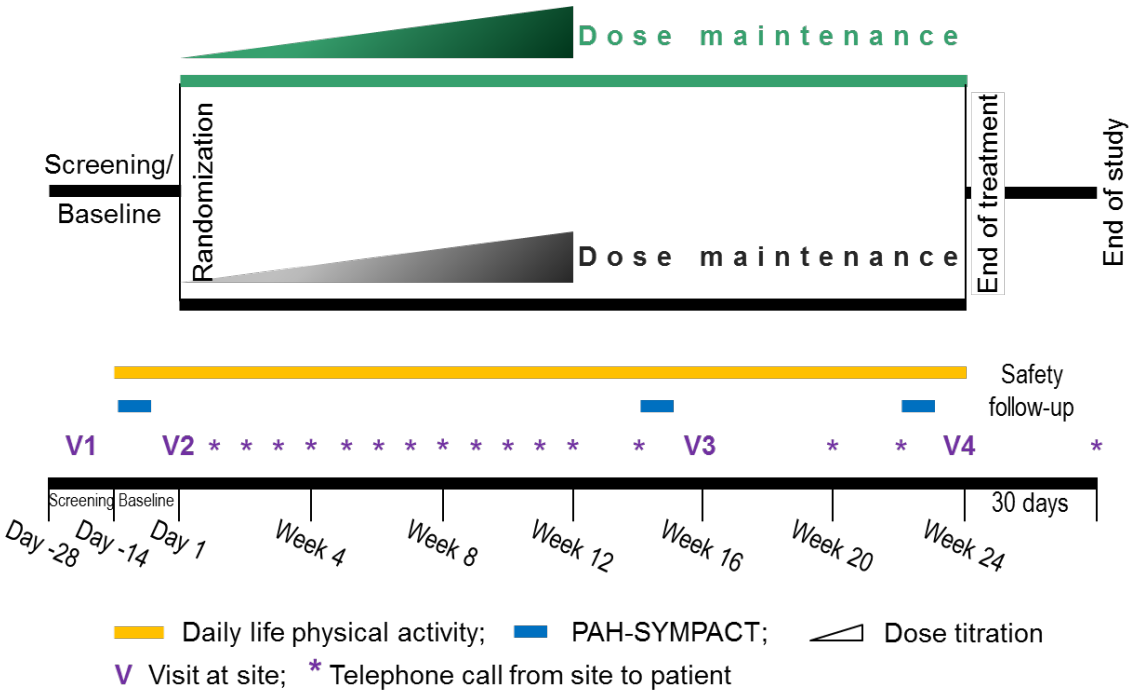
Post-treatment safety follow-up period (duration 30 days): This period starts 1 day after EOT, defined as the last day of intake of study drug. Patients will be followed up by telephone regarding ongoing and new AEs at investigator's discretion. The period is completed by an end-of-study (EOS) telephone call 30 days after EOT. This telephone call represents the end of the patient's study participation.

At any time during the study, unscheduled telephone calls or visits at the study site may be conducted if medically indicated at the discretion of the investigator.

The visit schedule and protocol-mandated assessments are displayed in Table 1 and Table 2 and described in Sections 7 and 8.

The overall study design is depicted in [Figure 1].

Figure 1 Study design



3.1.2 Study duration

The study starts with the first act of recruitment (i.e., first Informed Consent Form [ICF] signed) and ends with the last visit of the last patient. Patients will be treated for 24 weeks or less in case of premature discontinuation of the study treatment.

Patients enter a post-treatment observation period which lasts until 30 days after EOT to collect safety information. For an individual patient, the EOS is marked with a telephone call from the site at the end of the 30-day safety follow-up. The duration of study participation of a patient is about 7.5 months from ICF signed to EOS.

3.2 Study design rationale

The primary objective of this study is to evaluate the effect of selexipag on patient's DLPA. A placebo-controlled study design was chosen since several medication-independent factors may have an influence on DLPA, such as changes in duration of day light, weather conditions, season, and motivational effect by the use of an actigraphy device during the course of the study. The placebo control will thus allow for the non-confounded evaluation of the treatment effect of selexipag on DLPA, but also on the patient reported PAH symptoms and their impacts on daily life.

The use of placebo is considered safe and ethically justified because patients are required to be on background PAH therapy proven to be effective (Section 4.2).

Selexipag is titrated to the patient's individualized HTD during 12 weeks as per the pivotal Phase 3 trial GRIPHON. Titration includes time periods during which the patient does not receive the effective dose and/or experiences transient side effects. Both may affect DLPA adversely. Therefore, a subsequent time period of additional 12 weeks during which the patient receives the individual optimal dose is considered appropriate to assess DLPA and PAH-SYMPACT® under conditions reflecting maintenance therapy.

3.3 Study committees

A Steering Committee has been appointed by Actelion to contribute to the design of the protocol, the oversight of study conduct, the evaluation of results, and the support in publication. The committee is governed by a Steering Committee charter.

4 PATIENT POPULATION

4.1 Patient population description

This study will enroll adult male and female patients aged 18 to 75 with Group I PH [Galiè 2015a], except subgroups 1.4.3 (Portal hypertension) and 1.4.5 (Schistosomiasis), and except patients of subgroup 1.4.4 (Congenital heart disease) with other than corrected simple congenital heart defects.

Patients must be in WHO FC II and III, stably treated with an endothelin receptor antagonist (ERA), and must have no significant pulmonary or cardiac concomitant diseases as detailed in Sections 4.3 and 4.4.

Eligible patients must be able and willing to give informed consent for participation in the clinical study.

4.2 Rationale for the selection of the study population

The study population was selected based on the United States Product Information (USPI) and the EU Summary of Product Characteristics (SmPC) indication for Uptravi®. Patients with significant cardiovascular, pulmonary, immunological, hepatic, or ophthalmological medical conditions or therapies are excluded since they could potentially be at greater risk of experiencing side effects, and/or their conditions could interfere with evaluation of the treatment effect, study assessment and interpretation of study results.

To ensure an appropriate treatment for patients assigned to placebo, all eligible patients are required to be on background PAH therapy with either an ERA or an ERA in combination with a drug targeting the nitric oxide pathway for at least 90 days and on a stable dose for 30 days prior to initiation of study drug. Two clinical trials have

demonstrated that an ERA either alone or in combination with a phosphodiesterase-5 (PDE-5) inhibitor significantly reduces morbidity events in patients with PAH [Pulido 2013, Galiè 2015b]. This evidence is not available for PDE-5 inhibitors and soluble guanylate cyclase (sGC) stimulators if administered as the only PAH specific therapy. Therefore, PDE-5 inhibitors and sGC stimulators are allowed only if administered concomitantly with an ERA for at least 3 months and on a stable dose for 30 days prior to initiation of study drug.

The safety and efficacy of selexipag in a pediatric population (< 18 years of age) have not been established. Patients above 75 years of age are excluded from the study due to potential age-related comorbidities that may interfere with PAH disease stability.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any patient:

1. Signed informed consent prior to initiation of any study mandated procedure.

2. Male and female patients with symptomatic PAH, aged from 18 years to 75 years inclusive.

   A woman of childbearing potential [see definition in Section 4.5.1] is eligible only if the following applies:

   a) Negative serum pregnancy test at Screening Visit 1 and a negative urine pregnancy test at randomization,
      AND
   b) Agreement to undertake monthly urine pregnancy tests during the study up to 30 days after study treatment discontinuation,
      AND
   c) Agreement to use an acceptable method of contraception [see definition in Section 4.5.2] from screening to 30 days after study treatment discontinuation.

3. Diagnosis of PAH belonging to one of the following subgroups of Group 1 PH according to the updated clinical classification [Galiè 2015a]:
   1.1. Idiopathic (IPAH)
   1.2. Heritable (HPAH)
   1.3. Drugs or toxins induced
   1.4. Associated (APAH) with one of the following:
      1.4.1. Connective tissue disease
      1.4.2. Human immunodeficiency virus (HIV) infection

1.4.4. Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) ≥ 1 year after surgical repair.

4. Documented hemodynamic diagnosis of PAH by right heart catheterization (RHC). Prior to randomization the most recently performed RHC at rest showing:

   a) mPAP ≥ 25 mmHg; and
   b) Resting PVR ≥ 240 dyn•s•cm^{-5} or 3 WUs; and
   c) PAWP or LVEDP ≤ 15 mmHg.

5. Treatment with an ERA for at least 90 days and on a stable dose for 30 days prior to randomization.

6. Possible treatment with a PDE-5 inhibitor or sGC stimulator must be ongoing for at least 90 days and on a stable dose for 30 days prior to randomization.

7. WHO FC II or III at randomization.

8. 6MWD ≥ 100 m at Visit 1.

9. Ability to walk without a walking aid.

10. Valid baseline data at Visit 2 for DLPA and PAH-SYMPACT® defined as:

    a. DLPA: Within the last 14 days (excluding Day 1), at least 9 days each with a minimum of 14 hours wear time;

       AND

    b. PAH-SYMPACT®: Of the 7-day PAH-SYMPACT® assessment period, 5 days with complete data of the symptom part and 1 day with complete data of the impact part.

4.4 Exclusion criteria

Patients must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any patient:

1. PH Groups 2–5 according to the updated clinical classification [Galiè 2015a], and PAH Group 1 subgroups that are not covered by the inclusion criterion 3.

2. Patients on a PAH-specific **monotherapy** targeting the nitric oxide pathway (i.e., PDE-5 inhibitor or sGC stimulator).

3. Patients treated with prostacyclin, prostacyclin analog, or prostacyclin receptor agonist) at any time prior to Day 1 (administration for vasoreactivity testing is

permitted; previous prostacyclin / prostacyclin analogs used intermittently for the treatment of digital ulcers or Raynaud's phenomenon are permitted if stopped > 6 months prior to Day 1).

4. Any hospitalization during the last 30 days prior to Visit 1.
5. Worsening in WHO FC during the last 30 days prior to Visit 1.
6. Severe coronary heart disease or unstable angina.
7. Myocardial infarction within the last 6 months.
8. Decompensated cardiac failure.
9. Ongoing severe arrhythmias.
10. Cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months.
11. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH.
12. Presence of one or more of the following signs of relevant lung disease at the last examination any time up to Visit 1:
    a) Diffusing capacity of the lung for carbon monoxide < 40% of predicted UNLESS computed tomography reveals no or mild parenchymal lung disease; OR
    b) Forced vital capacity < 60% of predicted[2]; OR
    c) Forced expiratory volume in one second < 60% of predicted[2].
13. Documented severe hepatic impairment (with or without cirrhosis) at Visit 1, defined as Child-Pugh Class C.
14. Documented severe renal insufficiency at Visit 1, defined as estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL.
15. Hemoglobin < 80 g/L (< 4.96 mmol/L) at Visit 1.
16. Known or suspected uncontrolled hyperthyroidism.

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

17. Known or suspected pulmonary veno-occlusive disease.
18. Ongoing or planned dialysis.
19. Body mass index (BMI) above 40 kg/m^2 at Visit 1.
20. Sitting SBP below 90 mmHg at Visit 1.
21. Treatment with a strong inhibitor of CYP2C8 (e.g., gemfibrozil).
22. Receiving or having received any investigational drugs within 90 days prior to Visit 1.
23. Participation in a cardio-pulmonary rehabilitation program based on exercise training within 8 weeks prior to Visit 1. Such program must not be started during the course of the study.
24. Concomitant life-threatening disease with a life expectancy of less than 12 months.
25. Known hypersensitivity to any of the excipients of the study treatment formulation.
26. Pregnancy, breastfeeding, or intention to become pregnant during the study.
27. Any factor or condition likely to impair adherence to protocol mandated procedures, as judged by the investigator.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3]).
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

The reason for not being of childbearing potential will be recorded in the electronic Case Report Form (eCRF).

4.5.2 Acceptable methods of contraception

Women of childbearing potential as defined in Section 4.5.1 must use reliable contraception from screening up to 1 month following discontinuation of the last study

treatment. Reliable contraception must be started from screening. The methods of contraception used (including non-pharmacological methods) must be recorded in the eCRF every 4 weeks.

The use of at least one of the following methods is accepted as reliable contraception:

1. Oral, implantable, transdermal, or injectable hormonal contraceptives or intrauterine devices with hormones;
OR

2. True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the patient;
OR

3. Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to screening);
OR

4. Sterilization of the male partner, with documented post-vasectomy confirmation of the absence of sperm in the ejaculate.

Rhythm methods, use of a condom by the male partner alone, use of a female condom or diaphragm alone are not considered acceptable methods of contraception for this study.

5 TREATMENTS

5.1 Study treatment

Study treatments are selexipag or placebo. Details and references are provided in Section 1.2.

5.1.1 Investigational treatment: Description and rationale

- INN: Selexipag.
- Formulation, strengths: Tablets of 200 micrograms (mcg).
- Route of administration: Oral (p.o.).
- Dose: 200 mcg to 1600 mcg. Titration to the patient's individual HTD.
- Regimen: One to 8 tablets twice daily (b.i.d.) (in the morning and in the evening). Exceptions from the twice daily dosing regimen are described in Section 5.1.3.1.

Dose, regimen, and titration scheme are in accordance with the IB for selexipag [Selexipag IB].

5.1.2 Matching placebo: Description and rationale

- INN: Not applicable.
- Formulation, strengths: Tablets of 200 mcg (matching appearance).
- Route of administration: p.o.
- Dose: 200 mcg to 1600 mcg. Titration to the patient's individual HTD.
- Regimen: One to 8 tablets b.i.d. (in the morning and in the evening). Exceptions from the twice daily dosing regimen are described in Section 5.1.3.1.

Dose, regimen, and titration scheme are in accordance with the IB for selexipag [Selexipag IB].

5.1.3 Study treatment administration

The film-coated tablets are to be taken orally in the morning and in the evening. To improve tolerability, it is recommended to take Uptravi with food and, at the beginning of each up-titration phase, to take the first increased dose in the evening.

The tablets should not be split, crushed or chewed, and are to be swallowed with water.

5.1.3.1 Individualized dose titration (Weeks 1 to 12)

Each patient should be up-titrated to the individually HTD, which can range from 200 micrograms given b.i.d. to 1600 micrograms given b.i.d. (individualized maintenance dose [IMD]).

The starting dose is 200 mcg given b.i.d., approximately 12 hours apart. The dose is increased in increments of 200 mcg b.i.d., usually at weekly intervals. At the beginning of treatment and at each up-titration step it is recommended to take the first dose in the evening. During dose titration some adverse reactions, reflecting the mode of action of the study treatment (such as headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing), may occur. They are usually transient or manageable with symptomatic treatment. However, if a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level.

In patients in whom up-titration was limited by reasons other than adverse reactions reflecting the mode of action of study treatment, a second attempt to continue up-titration to the HTD up to a maximum dose of 1600 mcg b.i.d. may be considered until Week 12.

For every dose change, the end date of the previous dose and the start date of the new dose are recorded on a dedicated page in the eCRF.

A once-daily regimen (1 to 8 tablets once in the morning or in the evening) is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite.

In case of concomitant administration of a moderate inhibitor of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide) the dosing frequency of selexipag/placebo should be reduced to once daily because of drug-drug interactions. A drug-drug interaction study showed that clopidogrel had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite approximately 2.7-fold at steady-state. The dosing frequency should be reverted to twice daily when co-administration of the moderate CYP2C8 inhibitor is stopped [Selexipag IB].

In case of concomitant administration of a moderate inducer of CYP2C8 (e.g., rifampicin), dose adjustment of selexipag/placebo may be required because of drug-drug interactions. Specifically, rifampicin did not lead to a relevant change in exposure to selexipag, whereas exposure to the active metabolite decreased by half [Selexipag IB].

Table 3 Recommended double-blind up-titration scheme

Duration (Study Days)[1]	Dose regimen[2, 3, 4]	
Day 1 to Day 7	200 mcg twice daily	(1 tablet twice daily)
Day 8 to Day 14	400 mcg twice daily	(2 tablets twice daily)
Day 15 to Day 21	600 mcg twice daily	(3 tablets twice daily)
Day 22 to Day 28	800 mcg twice daily	(4 tablets twice daily)
Day 29 to Day 35	1000 mcg twice daily	(5 tablets twice daily)
Day 36 to Day 42	1200 mcg twice daily	(6 tablets twice daily)
Day 43 to Day 49	1400 mcg twice daily	(7 tablets twice daily)
Day 50 to Day 56	1600 mcg twice daily	(8 tablets twice daily)

[1] Duration is indicated to guide the recommended weekly up-titration. Intervals may be prolonged based on tolerability considerations. The individualized dose titration should be completed no later than Day 85 (Week 12).
[2] Or highest tolerated dose. The indicated doses are target doses if previous dose level was tolerated or if tolerability issues were addressed by down-titration.
[3] The first dose within a period may be taken in the evening only, i.e., once a day.
[4] Exceptions from the twice daily dosing regimen are described in Section 5.1.3.1.

5.1.3.2 Individualized maintenance dose (Weeks 13 to 24)

The IMD is the HTD reached during individualized dose titration and should be maintained from Week 13 to Week 24. Change of study treatment dose is allowed if

needed for efficacy or safety/tolerability reasons. If the therapy over time is less tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered. The dose may be increased (to a maximum dose of 1600 mcg b.i.d.) if the patient may benefit from a higher dose, as judged by the investigator. For every dose change, the end date of the previous dose and the start date of the new dose are recorded on a dedicated page in the eCRF.

5.1.4 Treatment assignment

At Screening (Visit 1), patients will be assigned a study-specific subject number by the Interactive Response Technology (IRT) system. This number consists of 4 digits identifying the site and 3 digits identifying the patient and is kept throughout the study and is the main subject identifier. In case of re-screening, the original number will also be used the second time.

After having verified that the patient meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT system at Visit 2 to randomize the patient. The IRT assigns a randomization number to the patient (in addition to the subject number mentioned above) and assigns the treatment kit numbers, which matches the treatment arm assigned by the randomization list to the randomization number. The randomization list is generated by the independent CRO Almac, using IXRS 3.0.

Patients will be randomized in a 1:1 ratio to either selexipag or placebo. Treatment allocation will be stratified by region, i.e. Europe/rest of the world vs. North America.

5.1.5 Blinding

This study will be performed in a double-blind fashion. The investigator and study personnel, the patients, the Clinical Research Associates (CRAs), Actelion personnel, and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until study closure. Actelion personnel responsible for clinical study supply distribution will need to be unblinded to ensure adequate supply of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file and they will not take part in any Clinical Trial Team (CTT) meetings after study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons, who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure, in accordance with Actelion Quality System (QS) documents.

5.1.6.2 Unblinding for interim analyses

Not applicable.

5.1.6.3 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a patient participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The treatment assignment will not be communicated to site personnel or to the Actelion CTT. Unblinded SUSAR information will be provided to respective health authorities and independent ethics committees (IECs) or institutional review board (IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.4 Emergency procedure for unblinding

The investigator, study personnel and Actelion personnel must remain blinded to the patient's treatment assignment. The identity of the study treatment may be revealed only if the patient experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded treatment assignment through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible, and if it does not interfere with or delay any decision in the best interest of the patient, the investigator is invited to discuss the intended unblinding with Actelion personnel.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, Actelion personnel must be informed as soon as possible before or after the unblinding.

The circumstances leading to unblinding must be documented in the Investigator Site File (ISF) and eCRF.

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

Study treatment is provided as tablets and supplied in childproof bottles of 120 tablets.

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

5.1.7.2 Study treatment distribution and storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label.

5.1.7.3 Study treatment dispensing

The patients will receive sufficient study treatment to cover the period up to the next scheduled visit. Patients are asked to return all used, partially used, and unused study treatment bottles at each visit. The protocol-mandated study-treatment dispensing procedures may not be altered without prior written approval from Actelion.

Once treatment is assigned to the patient as described in Section 5.1.4, the IRT system allocates the treatment kit numbers matching the treatment arm assigned by the randomization list, for the titration period and start of maintenance period until Week 16.

Likewise at Visit 3 (Week 16), the investigator/delegate contacts the IRT system which assigns the treatment kit numbers based on the patient's HTD for the maintenance period until Visit 4 (Week 24).

The same process will be performed in IRT at unscheduled visits in the specific dedicated module, for additional kit number assignment when applicable.

An accurate record of the date and amount of study treatment dispensed to each patient must be available for inspection at any time.

5.1.7.4 Study treatment return and destruction

On an ongoing basis and/or on termination of the study, the CRA will collect used and unused treatment kits, which will be sent to the warehouse, where Actelion personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by Actelion personnel or the deputy, and written permission for destruction has been obtained from Actelion. The protocol-mandated study treatment return procedures may not be altered without prior written approval from Actelion.

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

The inventory of study treatment dispensed to and returned by the patient (i.e., study-treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. It is to be recorded by site personnel on the study-treatment dispensing and accountability log and in the eCRF, and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (i.e., bottle) dispensed to the patient:

- Dispensed bottle number
- Date dispensed, and number of tablets dispensed (prepopulated in eCRF)
- Date returned, and number of tablets returned

Each medication bottle will have a label with a tear-off part specifying the study protocol number and the batch number. When the medication is issued to the patient, the investigator or pharmacist must remove the tear-off part and affix it to the Drug Dispensing Log.

All study treatment supplies, including partially used or empty bottles must be retained at the site for review by the CRA.

If the patient forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any tablets from the remaining study treatment bottle and to return it at the next visit.

5.1.8.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated at Visit 4/EOT for the period between Visit 3 and Visit 4 using the below formula:

Compliance = [(number of tablets dispensed at Visit 3 – number of tablets returned at Visit 4) / Total number of tablets that should have been taken during the period] × 100.

The number of tablets that should have been taken is derived from the HTD.

Compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as a protocol deviation.

5.1.9 Study treatment dose adjustments and interruptions

Dose adjustments are allowed if needed for efficacy or tolerability reasons at the discretion of the investigator. The end date of the previous dose and the start date of the new dose are recorded for every dose adjustment on a dedicated page in the eCRF.

If a dose of medication is missed, it should be taken as soon as possible. The missed dose should not be taken if it is almost time for the next scheduled dose (within approximately 6 hours).

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. If study treatment is missed or interrupted for 3 days or more, study treatment should be re-started at a lower dose at the discretion of the investigator, and then titrated to HTD [Section 5.1.3.1].

If the dose is adjusted or study treatment intake is interrupted for more than 1 day by the patient for any reason, she/he must immediately inform the investigator.

Study treatment interruptions greater than 1 day must be recorded in the eCRF.

Study treatment interruptions exceeding 2 consecutive weeks must lead to permanent discontinuation of study treatment.

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the patient, the investigator, or Actelion personnel. The main reason and whether discontinuation of study treatment is the decision of the patient (e.g., tolerability- or efficacy-related), the investigator (e.g., due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy), or Actelion (e.g., study terminated) must be documented in the eCRF.

A patient has the right to discontinue study treatment at any time, without any justification, by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study [see Section 9.2]). Although a patient is not obliged to give his/her reason for withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continued administration would be contrary to the best interests of the patient.

Study-specific criteria for discontinuation of study treatment are described in Section 5.1.11.

A patient who prematurely discontinues study treatment is NOT considered as withdrawn from the study. The patient will be asked to return for the EOT visit within 10 days of last intake of study treatment and to have a 30-day safety follow-up period after EOT. The period is completed by the EOS telephone call. This telephone call represents the end of the patient's study participation.

A patient who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Withdrawal of consent must lead to permanent discontinuation of study treatment. Patients who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of patients withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

5.1.11 Study-specific criteria for interruption / permanent discontinuation of study treatment

Study treatment interruptions exceeding 2 consecutive weeks must lead to permanent discontinuation of study treatment.

5.1.11.1 Hemoglobin abnormalities

If there is a decrease in hemoglobin from baseline[3] of > 20 g/L during the treatment period, a re-test must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

- Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), peripheral blood smear, reticulocyte count, iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation), lactate dehydrogenase, indirect bilirubin.

Study treatment must be temporarily interrupted if clinically mandated based on the investigator's judgment, or in any of the following situations:

- A decrease in hemoglobin to < 80 g/L (< 4.96 mmol/L),
- A decrease in hemoglobin from baseline of > 50 g/L (> 3.10 mmol/L),
- The need for transfusion.

Re-introduction of study treatment may be considered by the investigator if hemoglobin recovery, defined as a return of hemoglobin above the lower limit of the normal range or to baseline, is achieved.

[3] Baseline hemoglobin refers to the last hemoglobin value obtained prior to first intake of study treatment.

5.1.11.2 Severe hepatic impairment

If liver impairment is suspected, a clinical assessment of severity (e.g., Child-Pugh score) should be performed. If a severe hepatic impairment (e.g., Child-Pugh C) is diagnosed, the study treatment must be discontinued.

5.1.11.3 Start of a CYP2C8 inhibitor

Study treatment must be discontinued if a strong CYP2C8 inhibitor (e.g., gemfibrozil) is started.

In case of concomitant administration of a moderate inhibitor of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide), the dosing frequency of selexipag/placebo should be reduced to once daily because of drug-drug interactions. A drug-drug interaction study showed that clopidogrel had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite approximately 2.7-fold at steady-state. The dosing frequency should be reverted to twice daily when co administration of the moderate CYP2C8 inhibitor is stopped [Selexipag IB].

5.1.11.4 Pregnancy

If a female patient becomes pregnant while on study treatment, study treatment must be discontinued immediately, and a Pregnancy Form must be completed along with documentation on AE page in the eCRF [see Section 10.3].

5.1.11.5 Hyperthyroidism

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.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing of informed consent.

A therapy that is study-concomitant is any treatment that is ongoing at or initiated after signing of informed consent or initiated up to 30 days after EOT.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period.

5.2.2 Recording of previous/concomitant therapy

The use of all study-concomitant therapy (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded

in the eCRF. Previous therapy must be recorded in the eCRF if discontinued less than 3 months prior to signing of the informed consent. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, and indication will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

Single-dose administration of a drug for vasoreactivity testing during RHC is allowed.

Cardio pulmonary rehabilitation programs based on exercise starting after Visit 4 (Week 24) are allowed.

5.2.4 Forbidden concomitant therapy

Gemfibrozil, a strong CYP2C8 inhibitor, has been shown to increase the exposure of selexipag and its active metabolite significantly. Hence, concomitant administration of selexipag and strong inhibitors of CYP2C8 (e.g., gemfibrozil) is forbidden.

Cardio pulmonary rehabilitation programs based on exercise ongoing or initiated at any time from 8 weeks prior to Visit 1 until Visit 4 (Week 24) are forbidden.

5.2.5 Rescue therapy

In the event of documented worsening of PAH, it is permitted to use prostacyclin, prostacyclin analogs, or prostacyclin receptor agonists as rescue therapy, in parallel to discontinuation of double-blind study treatment. Start of rescue therapy and discontinuation of double-blind selexipag or placebo may overlap in order to ensure sustained efficacy during the transition. Patients starting rescue therapy remain in the study until EOS, i.e., Week 24/EOT +30 days.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint(s)

The primary efficacy variables are:

- Change from baseline to Week 24/EOT in actigraphy-assessed DLPA as measured by:
  - Daily time spent (minutes) in non-sedentary activity (> 100 activity counts per minute)
  - Percentage of daily time spent in non-sedentary activity (> 100 activity counts per minute)
  - Total DLPA in counts/min
  - Sleep: Total sleep time (TST; minutes), wake after sleep onset (WASO; minutes), number of awakenings, sleep efficiency (percentage)

The study is designed as exploratory, and therefore all actigraphy variables are listed under primary endpoints.

6.1.2 Secondary efficacy endpoints

The secondary efficacy variables are:

- Change from baseline to Week 24/EOT for following PAH-SYMPACT® domain scores:
  - Cardiovascular symptom domain score
  - Cardiopulmonary symptom domain score
  - Physical impact domain score
  - Cognitive/emotional impact domain score
- Change from baseline to Week 24/EOT for following variables:
  - WHO FC
  - 6MWD
  - Borg dyspnea index at 6MWT
  - N-terminal pro b-type natriuretic peptide (NT-proBNP)

6.1.3 Other efficacy endpoints

The other efficacy variables are:

- Change from baseline to Week 24/EOT for blood biomarkers associated with, e.g., PAH worsening, right/left ventricle function, and inflammation.
- Association between actigraphy variables and other efficacy endpoints (PAH-SYMPACT®, 6MWD, etc.).

6.2 Safety endpoints

The safety and tolerability endpoints are:

- Treatment-emergent AE[4] and SAEs up to 30 days after study treatment discontinuation.
- AEs leading to discontinuation of study treatment.
- Change from baseline in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points during the study.

[4] A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment start until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation.

6.3 Biomarkers

Based on nonclinical data [Gomez-Arroyo 2015], it is hypothesized that selexipag may have a beneficial effect on circulating biomarkers involved in right ventricular function and structure. Therefore, changes in such biomarkers from baseline to Week 24 will be explored. The list of biomarkers to be measured after the end of the study will be based on the latest scientific evidence regarding right ventricular function and structure at the time of laboratory analysis. No genetic testing of any kind will be performed.

7 STUDY ASSESSMENTS

All study assessments will be performed by a qualified study staff member: medical, nursing, or specialist technical staff, and recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF. Assessments will be performed at the appropriate visits or via telephone calls as indicated in the visit and assessment schedules in Table 1 and Table 2. If the principal investigator (PI) delegates any study procedure/assessment for a patient to an external facility, he/she should inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains the responsibility of the PI.

Calibration certificates for the temperature monitoring device for the study treatment storage area must be available prior to screening of the first patient at the site.

7.1 Patient characteristics

During Visit 1, the following assessments are to be obtained and recorded in the eCRF.

7.1.1 Informed consent signature (Visit 1)

- Prior to any study-mandated procedures.
- Original ICF to be kept in the site file.
- Date and time of informed consent signature to be entered in the eCRF.

7.1.2 Demographics (Visit 1)

- Age (in years).
- Race (if allowed by local regulations) and Ethnicity.
- Sex.

7.1.3 Documentation of PAH disease (Visit 1)

- Date of diagnosis.
- Etiology of PAH.
- Most recent RHC: Date, mPAP (mmHg), PAWP (mmHg) or LVEDP (mmHg) if PAWP not available, PVR (WU).

7.1.4 Medical history (Visit 1)

- Chronic and acute medical conditions.
- All previous medically important conditions.

7.1.5 Previous and concomitant therapies

Previous therapy (last dose, date of discontinuation) must be recorded in the eCRF if discontinued less than 90 days prior to informed consent signature.

- Concomitant medication start date, dose, route of administration, indication for which the medication is taken are to be recorded at Visit 1.
- Changes to be recorded at site visits and telephone calls.

7.1.6 Eligibility, randomization (Visit 1 and Visit 2)

Determination of eligibility: Eligibility criteria [see Section 4] are reviewed based on patient medical records, the assessments performed at Visit 1 and Visit 2, and valid baseline assessments for DLPA and PAH-SYMPACT®.

For patients who fail screening, the following assessments must be performed if possible and recorded in the eCRF at Visit 1 and/or Visit 2:

- Informed consent signature.
- Demographics.
- Reason for Screen failure.

An eligible patient is considered randomized if he/she is supplied with study treatment.

7.2 Efficacy assessments

7.2.1 6MWT and Borg dyspnea index

The 6MWT is a non-encouraged test, which measures the distance covered by the patient during a 6-minute walk [Appendix 1].

At Visits 3 and 4, the 6MWT is performed at trough levels of study treatment. Trough level of study treatment is defined as: the last dose has been taken not less than 8 hours prior to the 6MWT.

Borg dyspnea index is assessed immediately after the 6MWT. Dyspnea is rated by the patient according to the maximal shortness of breath experienced during the 6MWT [Appendix 2].

7.2.2 WHO FC

WHO FC will be assessed according to Appendix 3.

7.2.3 Daily life physical activity

The DLPA of the patient is assessed via the actigraphy device ActiGraph GT9X Link. The device is given to the patient at Visit 1 (Screening Visit), and the patient is instructed to wear the actigraphy device at the wrist of the non-dominant hand (ambidextrous patients may wear it at either wrist) during the entire study up to Week 24. Patient is instructed to upload data, i.e., epoch data, daily via the hand-held mobile device (same device as used for the PAH-SYMPACT®) to the vendor's server via a cellular connection. The submitted data will be used to monitor patient's compliance with device use and handling. Patients will be provided with a paper manual.

To ensure DLPA data quality, the epoch data received will be checked by the vendor. Should corrective actions be necessary, patients may be contacted either from the site staff (e.g., telephone call, text message) or via messages onto the hand-held mobile device from the vendor. At any time, the site and the CRA will have access to a patient report displaying patient's adherence to DLPA assessment.

The ActiGraph GT9X Link does not display collected data, i.e., the patients do not have access to their activity measurements since this could influence their behavior. At every site visit the study site transfers the complete data (raw data) from the ActiGraph GT9X Link to the vendor's server as described in the site manual. The raw data will be transferred to Actelion Pharmaceuticals Ltd. at the end of the study.

Patients must return the ActiGraph GT9X Link to the site at EOT. The devices will be returned to the vendor. The patient is provided with a report (on paper) summarizing the patient's individual activity levels during his/her participation in the study.

7.3 Safety assessments

7.3.1 Vital signs

- Sitting SBP and diastolic blood pressure (DBP) (mmHg), measured (always at the same arm) after at least 5 minutes of rest in a sitting position.

- Pulse rate (beats per minute), measured after at least 5 minutes of rest in a sitting position.
- Body weight (kg, lb).
- Body height (cm, inch), at Visit 1 only.
- BMI will be calculated and displayed automatically upon entry of weight and height in the eCRF.

7.3.2 AEs and SAEs

The patient will be asked at every visit and telephone call whether AEs occurred since the previous visit or telephone call. Any AEs or SAEs that occur after signing of the ICF will be recorded on AE pages in the eCRF. SAEs must also be reported on SAE forms. The definitions, reporting and follow-up of AEs, SAEs and pregnancies are described in Section 10. Pregnancies will be considered AEs for the purpose of recording pregnancies in the eCRF and must be reported on the Actelion Pregnancy form.

7.4 Laboratory assessments

7.4.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests (excluding urine pregnancy tests), including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be loaded into the clinical database, i.e., no entry into the eCRF is required for central laboratory data.

Eligibility of patients at screening may alternatively be determined using local laboratory tests as long as the central laboratory kit is used in parallel. Local laboratory results alone may be sufficient in other exceptional situations (e.g., patient is hospitalized in a different hospital due to a medical emergency). Local laboratory data including the normal ranges must be entered on dedicated eCRF pages. The investigator/delegate will provide Actelion with the name, professional degree, and *curriculum vitae* of the director of the local laboratory, a copy of the laboratory's certification, and the normal ranges for each laboratory test that is evaluated locally. These laboratory references must be updated whenever necessary.

If a central laboratory sample is lost or cannot be analyzed, the investigator/delegate will collect an additional sample as soon as possible to repeat the analysis, unless a local laboratory sample was collected within the same time window and these test results are available.

Central laboratory reports will be sent to the study site. In the event of specific laboratory abnormalities (pre-defined threshold values), the central laboratory will alert Actelion and the concerned study site.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate within 3 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of informed consent must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities detected after signing of informed consent must be reported as an AE or SAE as appropriate [see Section 10], and must be followed until the value returns to within the normal range or is stable, or until the abnormality is no longer clinically relevant.

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

7.4.2 Laboratory tests

The laboratory tests performed are:

- Hematology: basic panel.
- Clinical chemistry: basic panel.
- NT-proBNP.
- Circulating biomarkers involved in right ventricular function and structure: Blood samples will be collected at the central laboratory, shipped to Actelion at the end of the study, and stored at Actelion for up to 2 years after the last patient's last visit and destroyed after that date. The list of biomarkers to be measured after the end of the study will be based on the latest scientific evidence regarding right ventricular function and structure at the time of laboratory analysis. No genetic testing of any kind will be performed.
- Pregnancy tests: see Section 7.6.
- Thyroid function: Hyperthyroidism has been observed with selexipag. Thyroid function tests performed locally are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism. The test result and the normal range must be recorded in the eCRF.
- Other laboratory assessments: Additional laboratory assessments will be done at the discretion of the investigator if deemed medically justified. Laboratory assessments and the respective normal ranges must be recorded as conventional units in the eCRF.

7.5 Patient reported outcome PAH-SYMPACT®

The PAH-SYMPACT® is a novel PRO developed according to the FDA guidance [FDA 2009] for PROs specifically for patients with PAH.

The PAH-SYMPACT® has two main parts: symptoms and impact [Appendix 4]. The symptom part is a questionnaire completed daily for 7 consecutive days and contains 12 items. The patient is asked to rate each of the items for the past 24 hours.

The impact part has a 7-day recall period and is completed on the seventh day of the symptoms questionnaire data collection period. It contains 11 items pertaining to the impact of PAH.

The PAH-SYMPACT® questionnaire should be filled out in the evening, at approximately the same time of each day. If the start date of the collection period is missed, the PAH-SYMPACT® questionnaire can be started up to 3 days later. The questionnaire is administered in local language via an electronic Patient-Reported Outcome (ePRO) device (hand-held mobile device) that patients take home. Patients will be trained on the ePRO device by the site staff during Visit 1. Patients will receive a paper patient guide to take home. Data will be transferred daily to an electronic database immediately upon completion of the questionnaire via a cellular connection to the vendor. The data received will be checked for completion compliance.

The site will be informed if the questionnaire has not been completed as per protocol. Should corrective actions be necessary, patients may be contacted either from the site staff (e.g., telephone call, text message) or via messages onto the mobile device from the vendor.

At any time, the site and the CRA will have access to a web-based patient report displaying patient's compliance based on the specifications listed above for each day and summarized for each PAH-SYMPACT® data collection period. All ePRO data will be transferred to Actelion Pharmaceuticals Ltd at the end of the study.

At EOT patients must return the mobile device to the site. The devices will be returned to the vendor.

7.6 Additional assessments for women

7.6.1 Childbearing potential

The childbearing potential of a female patient will be assessed at Visit 1 and recorded in the eCRF. For definitions see Section 4.5.1.

7.6.2 Contraception check (women of childbearing potential only)

The used method of contraception will be recorded in the eCRF at Visit 1. Changes to the used method of contraception will be recorded at each visit and telephone call.

7.6.3 Pregnancy tests (women of childbearing potential only)

Serum pregnancy tests for women of childbearing potential must be performed at Visits 1, 3, and 4. The test result will be recorded in the eCRF. Urine pregnancy tests will be performed at Visit 2 and monthly up to at least 1 month after study drug discontinuation. Urine pregnancy tests will either be performed during a scheduled visit or at home by the patient within 3 days prior to the scheduled telephone call. The performance of urine pregnancy tests will be confirmed in the eCRF. The test result must be recorded in the patient's medical record (source data). A serum pregnancy test is mandatory if pregnancy is suspected during the course of the study.

8 VISIT SCHEDULE

For each patient there are 4 scheduled study visits at the study site (Visits 1, 2, 3, and 4; see [Table 1]. For all visits, the patients must be seen on the designated day within the allowed time window as indicated in Table 1. In case of permanent discontinuation of study treatment prior to Week 24, Visit 4, i.e., EOT Visit, must take place as soon as possible and no later than 10 days after the last dose of study treatment, if possible.

During the dose titration phase, i.e., up to Week 12, weekly telephone calls from the study site to the patient will be performed. During the dose maintenance phase, telephone calls from the study site to the patient are scheduled at Weeks 15, 20, and 23. There will be an EOS telephone call from the study site to the patient 30 days after EOT [Table 2].

Unscheduled site visits and telephone calls may be performed at any time during the study.

8.1 Site visits

8.1.1 Visit 1: Screening/re-screening

Screening starts with the signature of the informed consent. The patient is registered with the IRT system. The date on which the first screening assessment is performed corresponds to the date of the Screening visit. The visit includes the assessments as follows:

- Informed consent
- Demographics, PAH etiology
- Medical history

- Previous/concomitant therapies
- Vital signs (blood pressure [BP], heart rate [HR], body weight, height)
- WHO FC
- 6MWT/Borg dyspnea index
- Central laboratory tests: Hematology, clinical chemistry, NT-proBNP, biomarkers
- Women only: Assessment of childbearing potential
- Women of childbearing potential only: Contraceptive methods used, serum pregnancy test
- AE and SAE recording
- Eligibility

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

Patients who have signed informed consent when the randomization target has been met may still be randomized.

At Visit 1, the patient is being equipped with, and trained on, the actigraphy device ActiGraph GT9X Link and the ePRO device (hand-held mobile device). A paper manual is handed out to the patient. The patient ID is being registered within the applications for the ActiGraph and the mobile device on the vendors' internet platforms. Valid DLPA and PAH-SYMPACT® assessments performed between Visit 1 and Visit 2 are baseline assessments.

It is permitted to re-screen patients once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, invalid DLPA data, invalid PAH-SYMPACT® data). The rescreening visit must be performed within 28 days prior to randomization (Visit 2).

At re-screening, the informed consent process and signature, and all Visit-1 assessments need to be repeated, including NT-proBNP, but excluding the sampling for blood biomarkers (unless not collected at initial screening).

8.1.2 Visit 2: Randomization

Visit 2 is performed on the day of randomization, i.e., Day 1. Randomization is achieved via the IRT system. Actigraphy data are uploaded to the vendor server. At the end of the visit, sufficient study treatment is dispensed to the patient. The patient takes the first study treatment dose (1 tablet of 200 mcg) at the site. Study treatment is continued the following day, b.i.d. (morning and evening, preferably with food). the starting dose (200 mcg b.i.d.) of study treatment is recorded in the eCRF.

The assessments are [see also Table 1]:

- Concomitant therapies (changes only)
- Vital signs (BP, HR, body weight)
- WHO FC
- Women of childbearing potential: Contraceptive methods used, urine pregnancy test
- Eligibility (including DLPA and PAH-SYMPACT® validity of baseline assessment)
- AE and SAE recording

8.1.3 Visit 3: Intermediate Visit

Visit 3 is performed at Week 16, Day 113 (−4 to +7 days). Patient adherence to DLPA assessment and PAH-SYMPACT® completion are reviewed. Actigraphy data are uploaded to the vendor server. The patient should return any used and unused study treatment to the site at this visit. Any change in study treatment dose is recorded in the eCRF. The IRT system is used to assign study treatment supply to be dispensed to the patient.

The assessments are [see also Table 1]:

- Concomitant therapies (changes only)
- Vital signs (BP, HR, body weight)
- WHO FC
- 6MWT/Borg dyspnea index
- Central laboratory tests: NT-proBNP, biomarkers, serum pregnancy test (women of childbearing potential)
- Women of childbearing potential: Contraceptive methods used

- Study treatment compliance [see Section 5.1.8.2]
- AE and SAE recording

8.1.4 Visit 4: End of treatment visit

Visit 4 is performed at Week 24, Day 169 (−4 to +14 days). The visit must be scheduled at least 1 day after completion of the ePRO period scheduled from Day 155 to Day 161. After premature study treatment discontinuation, Visit 4 is performed within 10 days after EOT, if possible. Actigraphy data are uploaded to the vendor server. The patient should return any used and unused study treatment to the site at this visit. The Actigraph GT9X Link and the mobile device are returned to the site. The EOT is indicated in the eCRF and entered in the IRT system. The patient is provided with a report (on paper) summarizing the patient's individual activity levels during his/her participation in the study. The dose of the last study treatment intake is recorded in the eCRF.

The assessments are [see also Table 1]:

- Concomitant therapies (changes only)
- Vital signs (BP, HR, body weight)
- WHO FC
- 6MWT/Borg dyspnea index
- Central laboratory tests: Hematology, clinical chemistry, NT-proBNP, biomarkers, serum pregnancy test (women of childbearing potential).
- Women of childbearing potential: Contraceptive methods used
- AE and SAE recording

The investigator and the patient remain blinded towards the treatment assigned during the study (selexipag or placebo). If the patient and investigator decide to transition onto commercial selexipag (Uptravi®), every effort will be made to avoid any interruptions in the treatment, recognizing that the patients will need to be re-uptitrated and the uptitration will be guided by their clinician.

8.1.5 Unscheduled visits

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

In case of an IMD increase, the IRT system allocates additional treatment kit numbers to the patient during this visit. The results of any study procedures performed at an unscheduled visit must be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

8.2 Telephone calls

The schedule of telephone calls is shown in Table 2.

8.2.1 Weekly telephone calls up to Week 12

Weekly (+/−3 days) telephone calls from the study site to the patient will be performed starting 7 (+/−3) days after Visit 2. The investigator or delegate reviews the patient's compliance with the actigraphy device and the ePRO, and supports the patient in remaining compliant, e.g., reminder to charge the ActiGraph weekly. The investigator (or delegate) evaluates the tolerability of study treatment and guides its titration aiming at the HTD.

The assessments are [see also Table 2]:

- Concomitant therapies (changes only).
- AE and SAE recording.
- Study treatment dose changes.
- Women of childbearing potential only: changes in contraceptive methods used. Patient is asked to perform a urine pregnancy test at home at Weeks 4, 8, and 12 (Days 29, 57, and 85) within 3 days prior to the telephone call.

8.2.2 Telephone calls from Week 13 to Week 24

Telephone calls from the study site to the patient will be performed on the first day of Week 15 and Week 23 (Days 99 and 155) and at Week 20 (Day 141). The investigator or delegate reviews the patient's compliance with the actigraphy device and the ePRO, and supports the patient in remaining compliant, e.g., reminder to charge the ActiGraph weekly. The patient is reminded about the PAH-SYMPACT® assessment periods of Weeks 15 and 23.

The assessments are [see also Table 2]:

- Concomitant therapies (changes only).
- AE and SAE recording.
- Study treatment dose changes.

- Women of childbearing potential only: Changes in contraceptive methods used. Patient is asked to perform a urine pregnancy test at home within 3 days prior to the telephone call on Day 141.

8.2.3 Post-Treatment Safety Follow-up telephone call

The Post-Treatment Safety Follow-up period starts immediately after EOT defined as the last day of intake of study drug, and continues for at least 30 days (EOT +30 days). The Post-Treatment Safety Follow-up visit is conducted by telephone 30 days (+10 days window) after EOT and represents the EOS for the patient.

The assessments are [see also Table 1]:

- Concomitant therapies (changes only).
- AE and SAE recording.
- Women of childbearing potential only: changes in contraceptive methods used. Patient is asked to perform a urine pregnancy test at home within 3 days prior to the telephone call.

8.2.4 Unscheduled telephone calls

Unscheduled telephone calls from the site to the patient may be performed at any time during the study at the investigators discretion. In addition, unscheduled telephone calls may be required to support the patient in adhering to DLPA assessment, PAH-SYMPACT® completion, and home urine pregnancy tests.

9 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

9.1 Study completion as per protocol

A patient who completes at least 24 weeks of treatment and the 30-day follow-up period is considered to have completed the study as per protocol.

9.2 Premature withdrawal from study

Patients may voluntarily withdraw from the study without justification for any reason at any time. Patients are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a patient withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a patient from the study (without regard to the patient's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the patient. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study.

Patients are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. The site must take preventive measures to avoid a patient being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted in case the patient cannot be reached). If the patient cannot be reached, the site must make a reasonable effort to contact the patient, document all attempts, and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the patient's home), respecting the patient's right to privacy. If the patient is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason (if known) for premature withdrawal from the study, along with who made the decision (patient, investigator, or Actelion personnel) must be recorded in the eCRF, if known.

If for whatever reason (except death or loss-to-follow-up) a patient is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the patient, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the patients' medical records but it will not be collected in the eCRF. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator – in agreement with Actelion – must promptly inform all enrolled patients and ensure their appropriate treatment and follow-up, as described in Section 9.4. Actelion may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patients' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from Actelion, the investigator must promptly inform Actelion personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval / favorable opinion of the study, the investigator must promptly notify Actelion personnel and provide a detailed written explanation of the termination or suspension.

9.4 Medical care of patients after study completion / withdrawal from study

After the patient's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to patients what treatment(s) / medical care is necessary and available according to local regulations.

The investigator and the patient remain blinded towards the treatment (selexipag or placebo) assigned during the study (selexipag or placebo). If the patient and investigator decide to transition onto commercial selexipag (Uptravi®) at the end of study treatment, every effort will be made to avoid any interruptions in the treatment, recognizing that the patients will need to be re-uptitrated and the uptitration will be guided by their clinician.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a patient during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.

- Continuous persistent disease or symptoms present at study start that worsen following the signing of informed consent.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.
- Overdose, misuse, abuse of the study treatment and study treatment errors.

10.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

For AEs not ongoing at the start of study treatment, if the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required to be reported.

For AEs ongoing at the start of study treatment, if the intensity worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the patient. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 10.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by the investigator.

10.1.4 Recording of adverse events

All AEs with an onset date after signing of informed consent and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the eCRF.

10.1.5 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up information obtained after the patient's EOS visit / telephone call will not be collected by Actelion.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: Refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: Refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did

not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

10.2.2 Reporting of serious adverse events

All SAEs occurring after signing of informed consent up to 30 days after study treatment discontinuation must be recorded on AE pages in the eCRF and reported on an SAE form to Actelion Global Drug Safety (contact details are provided on the SAE form), regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures.

10.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after study treatment discontinuation must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the patient's EOS visit / telephone call must be reported to Actelion Global Drug Safety, but it is not recorded in the eCRF.

10.2.4 After the [30-day] follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to Actelion Global Drug Safety 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 treatment.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to Actelion Global Drug Safety within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the patient, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be sent to Actelion Global Drug Safety (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. Actelion Global Drug Safety personnel (or the CRO's drug safety personnel) may contact the investigator to obtain further information.

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

The expectedness of an adverse reaction is determined by Actelion in the reference safety information (RSI) section provided in the most recent version of the IB and its Amendment 1. Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR and must be reported by Actelion to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

The following SAEs are commonly seen in patients with underlying PAH disease and are therefore anticipated to occur in this patient population. These SAEs (unless fatal) do not require expedited reporting to Health Authorities, ECs/IRBs, and investigators: symptoms of PAH worsening/exacerbation/ progression, abdominal pain, anorexia, chest pain, cyanosis, diaphoresis, dizziness, pre-syncope, syncope, dyspnea, orthopnea, fatigue, hemoptysis, heart failure, hypoxia, palpitations, collapse, systemic arterial hypotension, and tachycardia. Like all other SAEs, these SAEs must be reported on an SAE form by the investigator to the Actelion Global Drug Safety within 24 hours of the investigator's first knowledge of the event, and be reported on the AE form of the eCRF.

10.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring after study start (i.e., signing of informed consent) up to 30 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to Actelion Global Drug Safety (see contact details provided on the Pregnancy form), and on an AE page in the eCRF.

10.3.2 Follow-up of pregnancy

Any pregnancies must be followed-up to their conclusion and the outcome must be reported to Actelion Global Drug Safety.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.2.2.

10.4 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the Actelion Clinical Team (in charge of ensuring patients' safety as well as data quality).

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CRO supervised by Actelion.

A Statistical Analysis Plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

11.1 Analysis sets

11.1.1 Screened Analysis Set

The Screened Analysis Set includes all patients who are screened and have a patient identification number.

11.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all patients randomly assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible:

- Patients are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received).
- All available data are included.

11.1.3 Per-protocol Analysis Set

The Per-protocol Analysis Set (PPS) comprises all patients who received study treatment and who complied with the protocol sufficiently to allow assessment of the treatment effects. Criteria for sufficient compliance include exposure to treatment, availability of measurements and absence of major protocol deviations that have an impact on the treatment effect. The full list of criteria will be detailed in the SAP before making the full randomization information available.

11.1.4 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment, and the analysis will be based on the actual treatment received.

11.1.5 Usage of the analysis sets

The primary efficacy analysis will be performed on the FAS based on treatment as randomized. Secondary and other efficacy analyses will also be performed on the FAS. The PPS will be used for sensitivity analyses for primary efficacy variables.

Safety analyses will be performed on the Safety Set based on treatment as received.

Patient listings will be based on the FAS, unless otherwise specified. Patient disposition will be described for the Screened Analysis Set.

11.2 Variables

All variables described thereafter are related to the endpoints defined in Section 6.

11.2.1 Primary efficacy variables

The primary efficacy variables are:

- Change from baseline to Week 24/EOT in actigraphy-assessed DLPA as measured by:
  - Daily time spent (minutes) in non-sedentary activity (> 100 activity counts per minute)
  - Percentage of daily time spent in non-sedentary activity (> 100 activity counts per minute)
  - Total DLPA in counts/min
  - Sleep: TST (minutes), WASO (minutes), number of awakenings, efficiency (percentage)

Furthers details on other actigraphy variables will be provided in the SAP.

11.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- Change from baseline to Week 24/EOT for following PAH-SYMPACT® domain scores:
  - Cardiovascular symptom domain score
  - Cardiopulmonary symptom domain score
  - Physical impact domain score
  - Cognitive/emotional impact domain score

- Change from baseline to Week 24/EOT for following variables:
  - WHO FC
  - 6MWD
  - Borg dyspnea dyspnea index at 6MWT
  - NT-proBNP

11.2.3 Other efficacy variables

The other efficacy variables are:

- Change from baseline to Week 24/EOT for blood biomarkers associated with, e.g., PAH worsening, right/left ventricle function, and inflammation.
- Association between actigraphy variables and other efficacy endpoints (PAH-SYMPACT®, 6MWD, etc.).

11.2.4 Safety variables

Safety variables are listed in Section 6.2.

An AE is defined as any event that is recorded on the AE eCRF module regardless of the onset date. Treatment-emergent events are those with onset date/time ≥ start date/time of study treatment and up to 30 days after EOT.

Laboratory analyses are based on data received from the central laboratory. All transferred central laboratory data are taken into account regardless of whether they correspond to scheduled or unscheduled assessments.

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

This study is designed as exploratory with the purpose to generate hypotheses on new endpoints. All analyses performed will be descriptive with summary statistics and associated 95% confidence intervals (CI) provided when applicable. Any p-value provided as result of a statistical model is to be considered as exploratory only.

No adjustment for multiplicity will be performed.

11.3.2 Analysis of the primary efficacy variables

All actigraphy variables will be summarized by period of 14 days: Baseline (last 14 days before first dose), Week 2 (Day 1–14), Week 4 (Day 15–28), and so on until Week 24 (Day 155–168) or EOT (last 14 days period on study treatment) in case of premature discontinuation. Any actigraphy data recorded after Day 168/EOT will not be considered in summary statistics and will be listed only.

11.3.2.1 Hypotheses and statistical model

As the study is designed as exploratory, no formal hypothesis will be tested.

For all actigraphy variables (continuous), change from baseline to Week 24/EOT will be analyzed using an analysis of covariance (ANCOVA) including terms for treatment and region, and baseline values as covariates. The differences in least square means between treatment and placebo, corresponding 2-sided 95% CI, and p-value will be provided.

All actigraphy variables will be also reported overtime with actual values, absolute change and percentage change from baseline at each time point (14 days periods).

Daily time spent and percentage of daily time spent will be also displayed according to activity categories "sedentary", "light", "moderate", "vigorous" and "very vigorous". The different intensity levels (cut points) ranging from sedentary to very vigorous are based on the Freedson Adult algorithm [Freedson 1998]: "Sedentary" (0–99 counts/min), "Light" (100–1951 counts/min), "Moderate" (1952–5724 counts/min), "Vigorous" (5725–9498 counts/min) and "Very Vigorous" (9499 + counts/min).

11.3.2.2 Handling of missing data

To be considered evaluable for a given time, actigraphy variables should have been measured for at least 7 complete days (consecutive or not) at a specific time period of assessment (baseline, Week 2, …, Week 24/EOT). A complete day is defined as a record of at least 7 awake hours of data.

The main analysis will consider the last time period available at Week 24/EOT evaluation (last observation carried forward). Further details will be provided in the SAP.

11.3.2.3 Main analysis

All actigraphy variables will be analyzed in same way on the FAS population using the model and summary statistics described in Section 11.3.2.1.

11.3.2.4 Supportive/sensitivity analyses

Supportive analyses based on the PPS will be provided. In addition, repeated measures mixed models will be used to evaluate the effect of selexipag relative to placebo over time.

Further supportive analyses will be described in the SAP.

11.3.2.5 Sub-group analyses

Subgroup analyses will be performed at least by region (randomization stratification factor). Additional subgroups analyses will be described in the SAP.

11.3.3 Analysis of secondary efficacy variables

All secondary analyses will be performed on the FAS.

11.3.3.1 PAH-SYMPACT®

All PAH-SYMPACT® domain scores (cardiovascular symptom domain score, cardiopulmonary symptom domain score, physical impact domain score, cognitive/emotional impact domain) will be reported as continuous variables over time with actual values, absolute change and percentage change from baseline at each time points.

For change from baseline to Week 24/EOT, the same analysis as for primary variables (ANCOVA described in Section 11.3.2.1) will be performed for the 4 PAH-SYMPACT® domain scores.

Further details will be provided in the SAP.

11.3.3.2 Others PAH related clinical outcomes

Others PAH related variables (6MWD, Borg dyspnea index) will be reported over time with actual values, absolute change and percentage change from baseline at each time points.

For change from baseline to Week 24/EOT, the same analysis as for primary variables (ANCOVA described in Section 11.3.2.1) will be performed for 6MWD and Borg dyspnea index.

WHO FCs will be described by shift tables from baseline to each time point. NT-proBNP will be described by summary statistics over time. In addition, change from baseline to Week 24/EOT in NT-proBNP (log-transformed) will be analyzed using an ANCOVA with factors for treatment group, region, and a covariate for baseline NT-proBNP (log-transformed).

11.3.3.3 Association between actigraphy and others efficacy endpoints

The association between actigraphy variables and others efficacy endpoints (PAH-SYMPACT® domain scores, 6MWD, NT-proBNP) will be described using correlations, scatter plots and regressions. Details will be provided in the SAP.

11.3.4 Analysis of the safety variables

All safety analyses will be performed on the Safety Set using descriptive statistics. All safety data will be listed, with flags for quantitative abnormalities. AEs in patients who were screened but not randomized will be listed.

11.3.4.1 Adverse events

A treatment-emergent AE is any AE temporally associated with the use of study treatment. The number and percentage of patients experiencing treatment emergent AEs and SAEs at least once will be tabulated by treatment group and by:

- Medical Dictionary for Regulatory Activities (MedDRA™) system organ class (SOC) and individual preferred term within each SOC, in descending order of incidence.
- Frequency of patients with events coded with the same preferred term, in descending order of incidence.

Furthermore, treatment-emergent AEs and SAEs will be tabulated as described above by severity and relationship to study treatment.

AEs leading to premature discontinuation of study treatment and AEs with outcome death will be summarized as described above.

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

For AEs occurring more than 30 days after discontinuation of the study treatment, a dedicated analysis will be described in the SAP.

11.3.4.2 Laboratory variables

Descriptive summary statistics by visit and treatment group will be provided for observed values and absolute changes from baseline, in both hematology and blood chemistry laboratory tests. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 30 days will be assigned to the most appropriate visit time point according to the best fitting time window for that assessment.

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

Marked laboratory abnormalities will be summarized for each laboratory variable by treatment group providing their incidence and frequency. Absolute values and changes from baseline of laboratory values during the course of the study will be summarized using the usual location and scale summary statistics by treatment group.

The number and percentage of patients with treatment-emergent laboratory abnormalities will be tabulated by treatment group.

11.3.4.3 Vital signs and body weight

Vital signs (BP, pulse rate), and body weight will be summarized at each study visit using summary statistics by treatment group for both absolute values and changes from baseline. Patients for whom no post-baseline value is available are excluded from the analysis of the changes from baseline in the Safety Set.

11.3.5 Exposure to study drug

Exposure to study drug will be described in terms of duration, HTD (defined as the dose at Week 12) and IMD (defined as the dose to which a patient was exposed for the longest duration during the maintenance period).

The duration of exposure is defined as the time elapsing between the study drug initiation and discontinuation, inclusive. The exposure time will be tabulated by treatment group using mean, median, standard deviation (SD), first and third quartiles, minimum and maximum. The cumulative distribution of exposure time by different class intervals will be tabulated to show the number and percentage of patients in each class interval. Count and percentages of patients within each HTD and IMD dose class will be tabulated by treatment group.

11.3.6 Baseline characteristics and concomitant medications

Continuous baseline variables and disease characteristics (e.g., age, height, weight, BMI, BP, pulse rate, 6MWT, Borg Dyspnea index and time from PAH diagnosis) will be summarized by treatment group using mean, median, SD, first and third quartiles, minimum and maximum.

Qualitative baseline variables and disease characteristics (e.g., gender and race, etiology of PAH, WHO FC, medical history, previous and concomitant medications) will be summarized by treatment group using counts and percentages. Individual patient listings will be provided by treatment group.

Previous and concomitant medications will be coded according to the latest available version of the WHO drug code and the anatomic therapeutic chemical class code. They will be summarized by type (i.e., previous and concomitant) and treatment group by tabulating the number and percentages of patients having received each treatment.

11.4 Interim analyses

Not applicable.

11.5 Sample size

There are no longitudinal data available for actigraphy variables in PAH patients. Therefore the study is designed as exploratory and the sample size is based on enrolment

capabilities: 100 patients will be randomized in total (50 in placebo group and 50 in selexipag group).

One of the primary variables is the difference between the two groups for the change from baseline to Week24/EOT for the number of daily minutes spent in non-sedentary activity. A number of 100 patients will provide an acceptable precision for associated width of 95% CI (assuming normal distributions) given scenarios of common SD ranging from 30 to 90 minutes [Table 4 below]. Calculations were made using software FAST version 4.

Table 4 Confidence interval (2-sided 5%) width assuming different scenarios of SD

Common SD for change from baseline in time spent (minutes) in non-sedentary activity	Confidence interval (2-sided 5%) width for difference between two groups for time spent (minutes) in non-sedentary activity
30	± 11.76
40	± 15.68
50	± 19.6
60	± 23.52
70	± 27.44
80	± 31.36
90	± 35.28

SD, standard deviation.

Those CI widths are indicative only, and the main analysis for actigraphy variables will be based on ANCOVA including terms for treatment and region, and baseline values as covariates.

12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timelines of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc, a web-based tool). The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data

(i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).

Entries recorded by the patient in the PAH-SYMPACT® questionnaire are considered source data. Site personnel will review and ensure completeness of the patients' entries.

Patient screening and randomization data will be completed for all patients (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each patient who enters the screening period of the study, an eCRF must be completed and signed by the investigator/delegate. If a patient withdraws from the study, the reason must be noted on the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On the eCRF or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to Actelion and any CROs, patients must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other identifier. The investigator/delegate must keep a patient identification code list at the site, showing the screening/randomization number, the patient's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the patients (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

The external service provider for actigraphy (ActiGraph) will not have access to personally identifiable patient information. The external service provider for the ePRO (ExcoIntouch) can receive personally identifiable information (private mobile phone number) if the patient agrees to this. This information is used to send study related messages (sent by ExcoIntouch) to the patient's private mobile phone. However, ExcoIntouch is obliged to keep the private mobile phone number confidential and not to share with anyone else, including Actelion.

12.3 Database management and quality control

eCRFs will be used for all patients. The investigators will have edit access to the site eCRF data until the database is closed. Thereafter, they will have read-only access. The eCRF must be kept current to reflect patient status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the problem and requesting

clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and/or a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

This process will continue until database closure.

Laboratory samples will be processed through a central laboratory and the results will be electronically sent to Actelion.

Data collected by the vendors of the ePRO and actigraphy device are owned by Actelion Pharmaceuticals Ltd. The data will be transferred to Actelion at the end of the study. The vendors will not use the data for any purpose not related to the conduct of the clinical study AC-065A404.

AEs are coded according to the latest MedDRA™ used by Actelion.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate Actelion QS docs. After database closure, the investigator will receive the eCRFs of the patients of his/her site (including all data changes made) on electronic media or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with the latest versions, respectively, ICH-GCP Guidelines, the principles of the "Declaration of Helsinki" (currently 2013 version), and with the laws and regulations of the country in which the study is conducted.

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the patient (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to the latest versions of the ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study and/or legally designated representative. The investigator/delegate must explain to patients that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific patient populations and of individual patients, as well as to the methods used to give the information. Adequate time shall be given for the patient and/or legally designated representative to consider his or her decision to participate in the study and it shall be verified that the patient has understood the information (e.g., by asking the patient to explain what is going to happen).

The ICF will be provided in the country local language(s).

Site personnel authorized to participate in the consent process and/or to obtain consent from the patient and/or legally designated representative will be listed on the Delegation of Authority form supplied by Actelion. A study physician must always be involved in the consent process.

The patient and/or legally designated representative and authorized site personnel listed on the Delegation of Authority form supplied by Actelion must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

A copy of the signed and dated ICF is given to the patient and/or legally designated representative; the original is filed in the site documentation. The informed consent process must be fully documented in the patient's medical records. This must include at a minimum the study reference, the patient number, the date and, if applicable, time when the patient was first introduced to the study, the date and, if applicable, time of consent,

who participated in the consent discussion, who consented the patient, and any additional person present during the consent process (e.g., patient's family member[s]), and the information that a copy of the signed ICF was given to the patient / legally designated representative.

If the site intends to recruit patients who are considered as vulnerable (e.g., patient cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure patient's rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before patients are recruited.

13.4 Compensation to patients and investigators

Actelion provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the patient in the event of study-related injuries will comply with applicable regulations.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the patient.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to Actelion or (overruling) local requirements.

All protocol deviations will be reported in the Clinical Study Report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

13.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into two different categories of documents: ISF and patients' source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

If the site is using an electronic/computerized system to store patient medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal and restricted access to study patients only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store patient medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The print-outs must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the patient's medical records or with the patient's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all patients but at least for some of them (e.g., first patient; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some patients) as per Actelion's instructions. If it were not possible for the

CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV.

The SIV must be completed before the site can start the screening of study patients. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on patient recruitment rate and critical data-collection times.

The PI must ensure that the eCRF is completed after a patient's visit (site visit or telephone call), and that all requested patient files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active patients and all follow-up issues have been resolved. In case a site does not enroll any patients, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

13.9 Investigator Site File

Each site will be provided with an ISF prior to the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of content listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from Actelion. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform Actelion.

If the PI will change, or if the site will relocate, the CRA must be notified as soon as possible.

13.10 Audit

Actelion's/CRO's representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Actelion's requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., patient records) and facilities.

13.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform Actelion (usually via the CRA) that such a request has been made.

The investigator and site personnel must cooperate with inspector(s) and allow access to all study documentation (e.g., patient records) and study facilities.

13.12 Reporting of study results and publication

Actelion will post the key elements of this protocol and the summary of results on Actelion's Clinical Trial Register and within the required timelines on publically accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by Actelion representatives and the Coordinating Investigator (or PI for single-center studies).

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

The Coordinating Investigator and the Steering Committee will review the analysis of the data and discuss the interpretation of the study results with Actelion personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement 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.

The list of authors of any publication of study results may include representatives of Actelion and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, Actelion may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

Actelion's Policy on Scientific Publications can be found at:
http://www.actelion.com/documents/corporate/policies-charters/policy-scientific-publications.pdf.

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15 APPENDICES

Appendix 1 Actelion guidelines for 6-minute walk test

Please note: Per study requirement, patients must be at trough levels for study treatment. Trough level of study treatment (selexipag) is defined as: the last dose has been taken not less than 8 hours prior to the 6MWT.

Background

This document is an adaptation from the American Thoracic Society (ATS) guideline on the 6MWT (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-17).

Tool description

- A self-paced test that measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD).
- Assesses the submaximal level of functional capacity.
- Evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.

Contraindications and safety issues

Absolute contraindications for the 6MWT include:

- Unstable angina and/or myocardial infarction during the previous month. Stable exertional angina is not an absolute contraindication for a 6MWT, but subjects with these symptoms must perform the test after using their antiangina medication, and rescue nitrate medication must be readily available.

Relative contraindications include:

- Resting HR of more than 120 beats/min after 10 minutes of rest.
- Uncontrolled hypertension: SBP of >180 mm Hg +/− DBP > 100 mm Hg.

A physician is not required to be present during the test. However, the technician administering the test must be certified in cardiopulmonary resuscitation, and training in related health care fields is desirable.

Testing needs to be performed in a location where rapid appropriate response to emergency is possible and a mean is in place enabling to call for help if needed. Access to a crash cart, as well as medications to treat angina, bronchospasm, and severe

shortness of breath must be available (e.g., aspirin, subligual nitroglycerine, oxygen, albuterol metered dose inhaler or nebulizer).

Care must be taken to evaluate safety in ambulation prior to the 6MWT, to ensure that the subject is safe to proceed.

Reasons for immediately stopping a 6MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance. Any reason for discontinuing the test needs to be recorded.

Pulse oximetry is optional. If it is performed, measure and record baseline HR and oxygen saturation and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. The oxygen saturation must not be used for constant monitoring during the exercise (no intra-test measurements). The technician must not walk with the patient to observe the oxygen saturation.

General Instructions

The 6MWT needs to be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be free of obstacles. If a suitable indoor corridor cannot be found, the test may be performed outdoors if the weather is comfortable. A permanent, dedicated course is ideal. The use of treadmill and a continuous course is not allowed.

The walking distance used for the test needs to be 30 meters (not shorter than 20 meters) in length. This distance needs to be marked every 3 meters. The turnaround point must be marked with a cone. A starting line, which marks the beginning and the end of each 60–m lap, needs to be marked on the floor using brightly colored tape. Ensure that the subject walks the same course on each re-test.

The staff member administering the 6MWT needs to stand near the starting line during the test and must not walk with the subject, and not get distracted during the conduct of this test (e.g., talk to anyone). Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest, he/she may pause, lean against the wall and continue walking whenever he/she feels able. The 6-minute timer must continue to run even if the subject stops to rest. The test can be stopped at any moment as outlined under contraindications and safety issues.

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

For an individual subject, repeat testing must always be conducted under the same conditions throughout the clinical trial (e.g., same corridor). Whenever possible, repeat testing for an individual subject needs to be conducted by the same tester, and preferably at about the same time of the day to minimize variability. A warm up period before the test must not be performed.

Training tests

For subjects who have never performed a 6MWT previously, a training test is recommended before the 6MWT, due to a learning effect when performing the test.

Timing

The interval between training tests must be at least 1 hour, and the interval between training and Screening tests must be at least 2 hours. More than two 6MWTs cannot be performed on the same day.

Required equipment

Emergency call tool
Countdown timer (or stop watch)
Mechanical lap counter
Two small cones to mark the turnaround points
A chair that can be easily moved along the walking course
Worksheets on a clipboard
Sphygmomanometer
Automated electronic defibrillator
Source of oxygen
Oximeter (optional)

Subject preparation

Medications type, dose and number of hours taken before the test must be recorded. Restrictions in medications need to be described. Certain medications need to be stable prior to the test (oxygen, diuretics, etc.).

The subject needs to wear comfortable clothing and appropriate walking shoes.

The meals preceding the test need to be light, and the subject must not have exercised vigorously within 2 hours of beginning the test.

The subject needs to sit at rest for at least 10 minutes before the test starts.

Subjects must receive their usual medication on the day of the test. If the subject is used to taking bronchodilators before a walk, he/she must take them 5–30 min before the test.

If a subject is oxygen dependent, it is recommended that oxygen is delivered in the same way (i.e., same application route and/or delivery device and same way of carrying the delivery device) and the flow rate remains constant. However, from 1 hour prior to each 6MWT, until the completion of all assessments after the 6MWT, the flow rate must remain constant. Additionally, the same oxygen flow rate as the one administered during the 6MWT at screening, must be maintained throughout the clinical trial for each 6MWT, as well as the same way of carrying the delivery device.

Have the subject stand and rate their baseline dyspnea using the Borg scale and instructions.

Measurements

Measurement of the 6MWD – Instructions to the subject

The person administering the test uses the following exact dialogue with the subject:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

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

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. I will tell you when 2 minutes, 4 minutes have elapsed. Keep walking when I talk."

After these instructions are given to the subject, the person administering the test then asks:

"Do you have any questions about the test?"

"Please explain what you are going to do."

"Are you ready?"

"Start now, or whenever you are ready."

As soon as the subject starts to walk, the tester starts the timer and writes down start time.

The tester tells the subject the time elapsed by saying:

"You have 4 minutes to go."

"You have 2 minutes to go."

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

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

When the timer alarm rings the tester says:

"Stop!"

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

"You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer.

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

Ask subject: "What, if anything, kept you from walking farther?"

Record the post-walk Borg dyspnea index using the Borg scale and instructions.

If using a pulse oximeter, measure oxygen saturation and pulse rate from the oximeter.

Appendix 2 Borg dyspnea index

The Borg scale must be printed in well readable font size on paper.

At the beginning of the 6-minute walk test, show the scale to the subject and ask the subject this: "Please grade your level of shortness of breath using this scale."

As soon as possible following the walk test, remind the subject of the breathing grade that he/she chose before the exercise and ask him/her to rate his/her shortness of breath using the scale again. The tester uses the following dialog:

"I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg scale).

If there was no shortness of breath at all you would point to 0;

if the shortness of breath was not very great you would choose from 0.5 to 2;

if you were somewhat more short of breath you would select 3;

and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life."

Borg rating	Perceived exertion
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

Appendix 3 WHO Functional Classification of pulmonary hypertension

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

Appendix 4 PAH-SYMPACT® Questionnaire

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

The questionnaire and a patient manual will be available in the local language(s).

DAY 1

INSTRUCTIONS

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

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

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

DAYS 2-6 (Subsequent days prior to last day in week)

INSTRUCTIONS

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

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

DAY 7 (Last day of week)

INSTRUCTIONS

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

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

SYMPTOMS

1. In the past 24 hours …

Did you use oxygen?
☐0 No
☐1 Yes If yes: How many hours? _____

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

2. In the past 24 hours …

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

3. In the past 24 hours …

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

4. In the past 24 hours …

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

5. In the past 24 hours …

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

6. In the past 24 hours …

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

7. In the past 24 hours …

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

8. In the past 24 hours …

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

9. In the past 24 hours …

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

10. In the past 24 hours …

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

11. In the past 24 hours …

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

12. In the past 24 hours …

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

IMPACTS

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

1. In the past 7 days …

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

2. In the past 7 days …

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

3. In the past 7 days …

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

4. In the past 7 days …

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

5. In the past 7 days …

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

6. In the past 7 days …

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

7. In the past 7 days …

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

8. In the past 7 days …

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

9. In the past 7 days …

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

10. In the past 7 days …

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

11. In the past 7 days …

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