STATISTICAL ANALYSIS PLAN

FOR CSR OF PROTOCOL AC-065A404

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 (TRACE)

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Confidential

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS 8

1 INTRODUCTION 11
1.1 Study documents 11

2 STUDY DESIGN AND FLOW 11
2.1 Study design 11
2.2 Study visit and assessment schedule 12

3 OBJECTIVES 12
3.1 Primary objective(s) 12
3.2 Secondary objectives 12
3.3 Other objectives 13

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL 13
4.1 Changes to the analyses planned in the study protocol 13
4.1.1 Concomitant therapies 13
4.1.2 Treatment emergent definition and 30 days safety follow-up 13
4.1.3 Sub-group analyses 13
4.2 Changes in the conduct of the study / data collection 13
4.3 Clarifications concerning endpoint definitions and related variables or statistical methods 14
4.3.1 Windowed actigraphy data analysis 14
4.3.2 DLPA actigraphy endpoints 14
4.3.2.1 Daily time spent in non-sedentary activity 14
4.3.2.2 Total DLPA in counts/min 15
4.3.2.3 Sleep 16

5 DEFINITIONS OF VARIABLES 16
5.1 Screening failures 16
5.2 Patient characteristics 16
5.2.1 Demographics 16
5.2.2 Baseline disease characteristics 16
5.2.3 Medical history 17
5.2.4 Previous and concomitant therapies 17
5.2.4.1 Previous therapies 17
5.2.4.2 Baseline concomitant therapies 17

5.2.4.3 Concomitant therapies initiated during the study treatment period 17
5.2.4.4 PAH specific previous or concomitant therapies 17
5.3 Study treatment exposure and compliance 18
5.3.1 Exposure 18
5.3.1.1 Individual maximum tolerated dose (IMTD) 18
5.3.1.2 Individual maintenance dose (IMD) 19
5.3.2 Compliance with study treatment 19
5.3.3 Study treatment discontinuation 19
5.3.4 Study treatment adjustments or interruptions 20
5.4 Study discontinuation 20
5.5 Efficacy variables 20
5.5.1 Primary efficacy variables 20
5.5.1.1 Actigraphy DLPA endpoints in protocol 20
5.5.1.2 DLPA actigraphy endpoints 21
5.5.1.3 Sleep endpoints 23
5.5.2 Secondary efficacy variables 25
5.5.2.1 PAH-SYMPACT® domain scores: 25
5.5.2.2 WHO functional class 25
5.5.2.3 6-minute walk test 25
5.5.2.4 N-terminal pro b-type natriuretic peptide (NT-pro BNP) 26
5.5.3 Variables used for correlation analyses 26
5.6 Safety variables 26
5.6.1 Adverse events 26
5.6.1.1 Treatment-emergent adverse events 26
5.6.1.2 Frequency of treatment-emergent adverse events 26
5.6.1.3 Intensity of treatment-emergent adverse events 26
5.6.1.4 Relationship of treatment-emergent adverse events 27
5.6.2 Deaths 27
5.6.3 Serious adverse events 27
5.6.4 Adverse events leading to discontinuation of study treatment 27
5.6.5 Other significant adverse events 27
5.6.5.1 AEs of special interest (AESIs) based on the selexipag risk management plan (RMP) 27
5.6.5.2 AEs typical of prostanoid treatments 27
5.6.5.3 Non-serious AEs 27
5.6.6 Vital signs and body weight 27
5.6.7 Electrocardiogram 28
5.6.8 Laboratory 28
5.7 Quality of life variables 28

6 DEFINITION OF PROTOCOL DEVIATIONS 28

7 ANALYSIS SETS....29
7.1 Definitions of analysis sets....29
7.1.1 Screened analysis set....29
7.1.2 Full analysis set....29
7.1.3 Per-protocol analysis set....29
7.1.4 Safety analysis set....29
7.1.5 Other analysis sets....30
7.2 Usage of the analysis sets....30
8 DEFINITION OF SUBGROUPS....31
9 GENERAL STATISTICAL METHODOLOGY....32
9.1 Statistical models for continuous data....32
9.1.1 Analysis of covariance....32
9.1.2 Mixed model analysis with repeated measures....32
10 STATISTICAL ANALYSES....33
10.1 Overall testing strategy....33
10.2 General rules for data presentations....33
10.2.1 General guidelines for table contents....33
10.2.2 General guidelines for table layout and formats....34
10.3 Display of patient disposition, protocol deviations and analysis sets....34
10.3.1 Patient disposition....34
10.3.2 Protocol deviations....34
10.3.3 Analysis sets....34
10.4 Analyses of patient characteristics....35
10.4.1 Demographics....35
10.4.2 Baseline disease characteristics....35
10.4.3 Medical history....35
10.4.4 Previous baseline concomitant and concomitant therapies....35
10.5 Analysis of study treatment exposure and compliance....36
10.5.1 Exposure....36
10.5.2 Compliance with study treatment....36
10.5.3 Study treatment discontinuation....36
10.5.4 Study treatment adjustments and interruptions....36
10.6 Analysis of the primary efficacy variables....37
10.6.1 Hypothesis and statistical model....37
10.6.2 Main analysis....37
10.6.2.1 Analysis of DLPA actigraphy endpoints....37
10.6.2.2 Analysis of Sleep endpoints....38
10.6.3 Handling of missing data....39

10.6.4 Supportive/sensitivity analyses 40
10.6.4.1 Supportive analyses 40
10.6.4.2 Sensitivity analyses....40
10.6.4.3 Subgroup analyses 40
10.6.4.4 Compliance of DLPA endpoints 41
10.7 In case of notable unbalanced in compliance of DLPA, sensitivity analysis will be performed as mentioned in Section 10.6.4.2. In addition, the impact of weekday and weekend activities may be explored on a few of actigraphy DLPA endpoints (e.g., top 3 DLPA actigraphy parameters shown stronger difference between treatment arms). Analysis of the secondary efficacy variables....41
10.7.1 Secondary endpoints....41
10.7.1.1 Hypothesis and statistical model 41
10.7.1.2 Statistical analysis 41
10.7.1.3 Handling of missing data 42
10.7.1.4 Supportive/sensitivity analyses 43
10.7.1.5 Subgroup analyses 43
10.8 Correlation Analysis....43
10.9 Analysis of safety variables....43
10.9.1 Adverse events 44
10.9.2 Deaths, other serious adverse events 44
10.9.2.1 Death....44
10.9.2.2 Serious adverse events....44
10.9.2.3 Adverse events leading to study treatment discontinuations ..45
10.9.2.4 Other significant adverse events....45
10.9.2.5 Summaries of AEs for Clinical Trial data disclosure....45
10.9.3 Laboratory tests 46
10.9.3.1 Laboratory tests over time....46
10.9.3.2 Marked laboratory abnormalities 46
10.9.3.3 Marked laboratory hepatic abnormalities 48
10.9.4 Vital signs and body weight....48
10.9.4.1 Vital signs and body weight over time 48
10.9.4.2 Marked blood pressure abnormalities....48
10.10 Analysis of quality of life variables 49

11 GENERAL DEFINITIONS AND DERIVATIONS....49

11.1 Study treatment start- and end date....49
11.2 Treatment emergent assessments or events....49
11.3 Study days 49
11.4 Duration in months....49
11.5 Baseline definition 49
11.6 Visit windows 49

11.7 Handling of selexipag/placebo dose titrations between morning and evening dose 50
11.8 Derivation of DLPA actigraphy endpoints....51
11.9 Scoring the PAH-SYMPACT® questionnaire 52
11.9.1 Symptoms....52
11.9.2 Impact 53

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS 54

12.1 Imputation of previous/concomitant medication and therapy dates ...55
12.1.1 Previous/concomitant medication and therapy start date....55
12.1.2 Previous/concomitant medication and therapy end date....55
12.2 Imputation of AE start and end dates....55
12.2.1 AE start date....55
12.2.2 AE end date 56
12.3 Imputation of other date fields....56
12.3.1 Date of PAH diagnosis....56

13 REFERENCES 57

14 APPENDICES 58

LIST OF TABLES

Table 1 ActiGraph's wrist-to-hip count conversion 15
Table 2 PAH-specific therapies 18
Table 3 Summary of primary endpoints 24
Table 4 Overview of the different analysis sets and their usage 30
Table 5 Actigraphy assessment time windows 38
Table 6 Time windows for analysis of association between DLPA endpoints and secondary endpoints 43
Table 7 Definition of marked laboratory abnormalities 47
Table 8 Time windows for efficacy assessments, at the exception of actigraphy 50
Table 9 Time windows for treatment-emergent safety assessments 50
Table 10 Illustrative example for handling of selexipag/placebo dose titrations over day 51
Table 11 Symptom scores domains 53
Table 12 Impact scores domains 54
Table 13 Study periods, visits at study site and assessments 69

LIST OF FIGURES

Figure 1 Study design 12
Figure 2 Possible patterns of PAH-SYMPACT® period at baseline 71

LIST OF APPENDICES

Appendix 1 Protocol synopsis and study visit assessment schedule 58
Appendix 2 Baseline for PAH-SYMPACT® Scores 71
Appendix 3 Adverse events of special interest 73
Appendix 4 Document history 74

LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
b.i.d.	Twice daily
BMI	Body mass index
CI	Confidence interval
CRO	Contract Research Organization
CSR	Clinical study report
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DLPA	Daily life physical activity
eCRF	Electronic case report form
EOS	End-of-study
EOT	End-of-treatment
ePRO	Electronic patient reported outcomes
ERA	Endothelin receptor antagonist
EudraCT	European union drug regulating authorities clinical trials
FAS	Full Analysis Set
FC	Functional class
GGT	Gamma-glutamyltransferase
HIV	Human immunodeficiency virus
HTD	Highest tolerated dose
IMD	Individual maintenance dose

IMTD	Individual maximum tolerated dose
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LVEDP	Left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
METs	Metabolic equivalents
MMRM	Mixed model of repeated measures
mPAP	Mean pulmonary arterial pressure
MVPA	Moderate-to-vigorous physical activity (Freedson '98)
NT-proBNP	N-terminal pro b-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PD	Protocol deviation
PDE5i	Phosphodiesterase-5 inhibitor
PDID	Protocol deviation identifier
PPS	Per-Protocol Analysis Set
PT	Preferred term
PVR	Pulmonary vascular resistance
q.d.	Once daily
RBC	Red blood cell count
RHC	Right heart catheterization
RMP	Risk management plan
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study data tabulation model
sGC	Soluble guanylate cyclase

SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamate-pyruvate transaminase
SMQ	Standardized MedDRA query
SOC	System organ class
TST	Total sleep time
ULN	Upper limit of the normal range
VM	Vector magnitude
WASO	Wake after sleep onset
WBC	White blood cell count
WHO	World Health Organization
WHO FC	WHO functional class
WHODRUG	WHO drug dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the derivation of efficacy and safety endpoints, the analyses and the presentation of analysis results and data for the clinical study report (CSR) of study AC-065A404 (TRACE).

Study data tabulation model (SDTM) datasets are provided by data management and are considered source data. Technical procedures and steps for processing these data and for implementing the definitions of variables for the purpose of the statistical analysis in analysis data model (ADaM) datasets are covered in the analysis datasets specifications document.

1.1 Study documents

The following study documents are used for the preparation of the SAP:

- Protocol AC-065A404, Final Version 2, dated 5 December 2018
- Electronic Case Report Form (eCRF), Version 009, dated 11 April 2019
- Protocol deviation code list, Version 4.0, dated 5 February 2020
- Pulmonary Arterial Hypertension - Symptoms and Impacts® (PAH-SYMPACT®) User Guide Version 1, dated March 2017
- Data Transfer Agreement (ActiGraph), Revision N, dated 21 November 2019
- Data Transfer Agreement (Laboratory), Version 8.0, dated 18 September 2019
- Data Transfer Agreement (ePRO: PAH-SYMPACT), Version 4.0, dated 13 September 2019
- Selexipag (Uptravi®) EU Risk Management Plan Version 7, dated 7 June 2019
- Definition of Marked Abnormalities in Laboratory Data (OTH-000005), Version 09, dated 1 November 2017

2 STUDY DESIGN AND FLOW

This section describes the general design aspects of the study. Further details can be found in the protocol synopsis in Appendix 1.

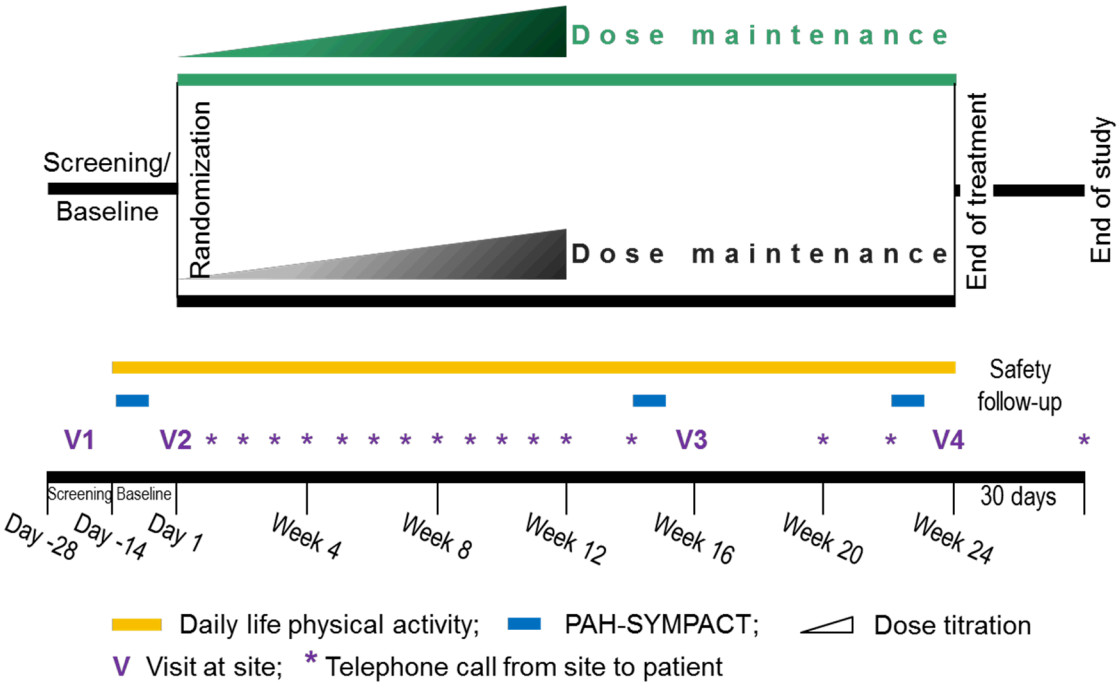
2.1 Study design

This is 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.

After signing informed consent, establishing study eligibility and a 14-day screening phase, patients will provide baseline efficacy data for 14 days before they return to the site for the baseline visit. At baseline visit, patients will be randomized in a 1:1 ratio to either selexipag or placebo double-blind treatment. Study drug will be up-titrated in weekly intervals to the highest tolerated dose, i.e., individual maximum tolerated dose (IMTD) after 12 weeks of treatment. At Week 16, the interim visit, and Week 24, the end of treatment (EOT) visit, the patients will return to the study center for efficacy and safety assessments. At Week 24,

during the EOT visit, study treatment will be discontinued. If the investigator believes that it is in the best patient's interest to transition to commercial selexipag (Uptravi®), in order to maintain the study treatment allocation blinded the patient will initiate Uptravi according to recommendations in the country specific approved labelling and Uptravi will be re-up-titrated under clinician's guidance. An end-of-study phone call will be made at the end of the safety follow-up phase 30 days after the EOT visit.

Figure 1 Study design



2.2 Study visit and assessment schedule

For the detailed visit assessment schedule refer to Table 13 in Appendix 1.

3 OBJECTIVES

3.1 Primary objective(s)

The primary objective of this study is to evaluate the effect of selexipag on daily life physical activity (DLPA) of patients with PAH.

3.2 Secondary objectives

The secondary objectives of this trial are:

- 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

3.3 Other objectives

Other objectives of this trial are to:

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

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

4.1.1 Concomitant therapies

Protocol section 5.2.1 defines concomitant therapies as study concomitant therapies, i.e., all therapy given at or after signature of informed consent are considered concomitant. An analysis using this definition would consider medications taken during the screening period as concomitant, which provides little scientific value. In this analysis, previous (i.e., ending prior to first study treatment intake), baseline concomitant, and concomitant (i.e., starting after first study treatment intake) medications will be analyzed. This approach is better suited to describing the population in terms of background therapy additional to study treatment and changes to the therapy during study drug intake [see details in Section 5.2.4].

4.1.2 Treatment emergent definition and 30 days safety follow-up

According to protocol section 6.2, adverse events (AEs) and serious adverse events (SAEs) from screening and up to 30 days after study treatment discontinuation are collected. The treatment-emergent AE definition refers to an AE which starts after study drug initiation and up to 3 days after end of study treatment, which is in line with the selexipag standard treatment emergent definition based on the consideration of the pharmacological half-life of selexipag's major metabolite (6.2–13.5 hours) and the analyses of previous selexipag clinical trials.

4.1.3 Sub-group analyses

Protocol section 11.3.2.5 defines the subgroup analyses that will be performed by region as a randomization stratification factor, i.e., and North America versus Europe/rest of the world. However, most patients are enrolled in the UK. The subgroup analyses will be based on UK versus non-UK. The originally planned subgroup by region North America versus Europe/rest of the world analysis will not be performed nor used in ANCOVA model.

4.2 Changes in the conduct of the study / data collection

None.

4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

4.3.1 Windowed actigraphy data analysis

Protocol section 11.3.2 states that actigraphy data collected after Day 168/EOT will not be used in the tabular summaries. This time limit does not include the allowed assessment window of −4 to +14 days during which the Week 24 visit should be conducted. For the actigraphy analysis, the EOT value of the actigraphy values will be the average of the last 14 days prior to the last dose of study drug, regardless of when the last dose is taken, i.e., before, at, or after EOT.

4.3.2 DLPA actigraphy endpoints

The protocol lists various actigraphy DLPA endpoints derived from the ActiGraph GT9X Link accelerometer data. The ActiGraph accelerometer measures accelerations in 3 axes (x-, y-, z-axis) at a sampling rate of 30 Hz. These raw acceleration data are processed in epochs of 60-seconds to generate activity counts per minute for each axis and for vector magnitude (sqrt [$counts_x^2$ + $counts_y^2$ + $counts_z^2$]) by ActiGraph's proprietary algorithms. The activity counts per minute are further summarized to daily values for each patient. In addition, each minute is classified as "wear" or "non-wear" and as well as for "awake" or "asleep". Wear time and non-wear time are classified by applying the Troiano algorithm [Troiano 2008]. Time awake and time asleep are classified by applying the Tudor-Locke algorithm [Tudor-Locke 2014].

The daily values, defined in the Data Transfer Agreement between ActiGraph and Actelion, are the basis for all DLPA endpoints including those for sleep.

4.3.2.1 Daily time spent in non-sedentary activity

For the purpose of the analyses, sedentary behavior is defined by an energy expenditure of ≤ 1.5 metabolic equivalents (METs) [Tremblay 2010]. Accordingly, non-sedentary activities considered all activities that are characterized by an energy expenditure of > 1.5 METs. Two thresholds for accelerometer-based activity counts corresponding to non-sedentary activities, i.e., > 1.5 METs, have been previously established:

- ≥ 100 y-axis counts per minute measured by a single-axis hip-worn ActiGraph accelerometer [Matthews 2008]. This is often referred to as one of the Freedson 98 thresholds in addition to those for light, moderate, vigorous and very vigorous activities [Freedson 1998].
- ≥ 1853 vector magnitude (VM) counts per minute measured by a triaxial ActiGraph accelerometer worn at the non-dominant wrist [Koster 2016].

In TRACE, the ActiGraph accelerometer is worn at the non-dominant wrist. Therefore, ActiGraph will apply a conversion algorithm from wrist counts to hip counts before applying the Freedson thresholds. The conversion algorithm is shown in Table 1:

Table 1 ActiGraph's wrist-to-hip count conversion

Wrist counts (WC)	Equivalent (hip) counts (EC)	WC as a function of EC
0 – 644	WC × 0.5341614	EC / 0.5341614
645 – 1272	WC × 1.7133758 – 759.414013	(EC+759.414013) / 1.7133758
1273 – 3806	WC × 0.3997632 + 911.501184	(EC-911.501184) / 0.3997632
3807 – infinity	WC × 0.0128995 + 2383.904505	(EC-2383.904505) / 0.0128995

Color coding: each color corresponds to a different Conversion Rule
Adapted from https://actigraphcorp.force.com/support/s/article/What-does-the-Worn-on-Wrist-option-do-in-the-Scoring-tab

The measurement of physical activity (PA) at the hip excludes manual PA, which may be a surrogate for QoL and mental health. Therefore, PA measured at the wrist is different from PA measured at the hip. It is unclear how well the wrist-to-hip conversion of activity counts takes the inherent difference between hip and wrist PA into account. No conversion is required for the 1853-VM count threshold. Since TRACE is an exploratory study, time spent in non-sedentary activity will be analyzed using both thresholds.

4.3.2.1.1 Daily time spent in moderate-to-vigorous physical activity

Time spent in moderate-to-vigorous physical activity (MVPA) is a fraction of time spent in non-sedentary activity. A recent communication by Bellerophon Therapeutics on the positive outcome of a Phase 2b clinical trial using the endpoint of daily time spent in MVPA [Nathan 2019] led to the decision to analyze MVPA in TRACE. Bellerophon's trial used a wrist-worn ActiGraph accelerometer, and MVPA was determined based on the Freedson 98 thresholds after count conversion from wrist to hip (see above). The threshold for MVPA is ≥ 1952 y-axis hip activity counts per minute corresponding to ≥ 2603 y-axis wrist activity counts per minute.

4.3.2.2 Total DLPA in counts/min

Total DLPA refers to the daily total activity counts obtained during the awaking time while the device was worn. To consider the acceleration data obtained from the wrist for all 3 axes, VM counts per minute will be analyzed.

4.3.2.2.1 Total DLPA in counts/min performed in non-sedentary activities

Total DLPA performed in non-sedentary activities is a fraction of the total DLPA in counts/min. Total DLPA performed in non-sedentary activities refers to the daily total VM activity counts per minute obtained during each minute of awaking time for which the device was worn and the VM counts per minute were ≥ 1853 counts [Koster 2016].

4.3.2.2.2 Total DLPA in steps per day

A recent study in 30 patients with PAH found that the change in daily step count correlated with a change in 6MWD (r = 0.43, p = 0.05) [Sehgal 2019]. ActiGraph's proprietary step counting algorithm will be used to analyze number of steps per day.

4.3.2.3 Sleep

Various algorithms are applied by ActiGraph to derive sleep variables.

Sleep episodes are determined by the Cole-Kripke Sleep Scoring Algorithm and may occur throughout the day [Cole 1992]. Sleep episodes of the night may be more relevant for the evaluation of sleep characteristics due to the circadian rhythm. Therefore, only sleep episodes starting from 7:00 pm to 06:59 am and ending no later than 11:59 am are considered in the analyses. To exclude non-wear time during sleep, each sleep episode must include at least 15 epochs with non-zero activity counts. The sleep variables, i.e., total sleep time, wake after sleep onset, and sleep efficiency, are obtained by applying the Tudor-Locke algorithm to each minute of a sleep episode [Tudor-Locke 2014].

5 DEFINITIONS OF VARIABLES

5.1 Screening failures

Screened patients are patients who received a patient number. Screen failures are patients who received a patient number but are not randomized.

If a patient is screened but not randomized, the reason for screen failure has to be collected in the eCRF. If a patient is re-screened and fails again, only the last reason for screening failure is analyzed.

5.2 Patient characteristics

5.2.1 Demographics

Demographics is collected at baseline and comprise age, sex, race, ethnicity, geographical region, systolic blood pressure (SBP), diastolic blood pressure (DBP), height and weight. Body-mass index (BMI) will be computed.

5.2.2 Baseline disease characteristics

Etiology of PAH, association of PAH with other diseases, and WHO functional class (WHO FC) are collected at baseline. The time since the initial diagnosis of PAH at the randomization date will be computed.

The documented results from the most recent right heart catheterization (RHC) confirming the diagnosis of PAH are collected: Mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP), and pulmonary vascular resistance (PVR). The time since the most recent RHC at the randomization will be computed.

A 6-minute walk test (6MWT) is performed at baseline. The Borg dyspnea score is assessed at the end of the test.

The baseline concomitant PAH specific therapy [see Section 5.2.4.2] will be summarized by category [see Table 2] in addition.

5.2.3 Medical history

Clinically significant diseases or medical conditions starting prior to the screening visit are collected. The start date of the disease or condition is collected together with the end date or the information if the condition is ongoing at screening visit or not.

Previous diseases are diseases which ended prior to the screening visit.

Study concomitant diseases are diseases which started prior to screening visit but were ongoing at the date of screening visit.

Medical history terms are coded using the most current version of the MedDRA dictionary at the time of the database closure.

5.2.4 Previous and concomitant therapies

All previous/concomitant therapies are coded using the WHODRUG dictionary.

5.2.4.1 Previous therapies

Previous therapies are any treatments for which the end date of treatment is prior to the first dose of study treatment.

All therapies which ended within 90 days prior to signature of informed consent are entered in the eCRF.

5.2.4.2 Baseline concomitant therapies

Baseline concomitant therapies are treatments that are initiated prior to start of study treatment and ongoing at the start date of study treatment.

5.2.4.3 Concomitant therapies initiated during the study treatment period

Concomitant therapies initiated during the study treatment period are therapies which were started with the study treatment or therapies which were started after the start of study treatment and before the last dose of study treatment.

5.2.4.4 PAH specific previous or concomitant therapies

All PAH specific previous or concomitant therapies are categorized by their mode of action (i.e., subcategory) as specified in Table 2 below.

Table 2 PAH-specific therapies

Category	Subcategory (mode of action)	Ingredient names
Antihypertensives for pulmonary arterial hypertension	ERAs	Ambrisentan, Bosentan, Sitaxentan, Macitentan
	PDE-5 inhibitors	Sildenafil, Tadalafil, Vardenafil
	sGC stimulator	Riociguat
Prostanoids		Epoprostenol, Treprostinil, Iloprost, Beraprost

Categories are identified by searching the coded WHODRUG preferred terms for occurrence of any of the ingredient names, e.g., 'Sildenafil' and 'Sildenafil Citrate' will both be assigned to PDE-5 inhibitors.
Sitaxentan has been removed from the market due to concerns about liver toxicity.

5.3 Study treatment exposure and compliance

Selexipag and placebo administered in double-blind fashion are considered as study drugs for this analysis.

5.3.1 Exposure

Study treatment is administered through two dosing periods.

- A titration period that starts at the day of randomization with the evening dose of a twice daily (b.i.d.) oral dose of 200 mcg, which is up-titrated on a weekly basis thereafter until the IMTD (maximum possible dose at 1600 mcg b.i.d.) is reached. The titration period ends at Day 86.
- A maintenance period, that follows the titration period, during which the dose of Selexipag/Placebo is maintained constant except dose adjustment for safety. The maintenance period starts at Day 87 and ends with the last dose of study treatment.

Both periods combined represent the overall exposure period.

Overall exposure to selexipag/placebo regardless of dose is defined as the number of days between the first dose and the last dose of selexipag/placebo medication, regardless of interruptions or titrations.

5.3.1.1 Individual maximum tolerated dose (IMTD)

The IMTD with unit mcg b.i.d is defined as the study drug dose taken by the patient at Day 87. If patients with study drug discontinuation prior to Day 87: 1) IMTD is defined as the highest daily dose (b.i.d) without reason for stop this dose level "dose reduction" or "discontinuation", or 2) If the daily dose (b.i.d) is only 200 mcg (i.e. no up-titration attempted) with the above reasons, IMTD is defined as zero.

If different doses of study drug are used on Day 87, the average dose is considered. If a patient receives study drug once daily (q.d.) instead of b.i.d., the following rule will be applied:

- During the concomitant treatment of moderate cytochrome P450 (CYP) 2C8 inhibitor (e.g., drug categorized in moderate or higher in the standardized drug grouping): Dose X mcg q.d. will be considered as equivalent to X mcg b.i.d. due to the drug-drug interaction.
- No concomitant treatment of moderate CYP2C8 inhibitor: Dose X mcg q.d. will be considered as equivalent to X/2 mcg b.i.d.

5.3.1.2 Individual maintenance dose (IMD)

For patients who enter the maintenance period, the IMD is defined as the daily study drug dose (mcg b.i.d.) to which the patient is exposed to for the longest time (i.e., maximum number of days including the interruptions) during the maintenance period, i.e., after Day 87. If more than one study drug dose corresponds to the maximum number of days during maintenance period, the highest dose is analyzed.

For patients with the last study drug dose intake prior to the maintenance period, the IMD is the highest study drug dose which did not lead to study drug discontinuation or down titration, regardless of the reasons for study treatment dose end on dose record(s) before or after the highest dose.

For patients who received only the lowest study drug dose level of 200 mcg b.i.d., the IMD is 200 mcg if study drug was not discontinued prematurely; otherwise it is set to 0 mcg.

For each patient, the following study drug doses (mcg b.i.d.) will be analyzed:

- Highest and weighted-average study drug dose in the titration period
- Highest and weighted-average study drug dose in the maintenance period (for patients who entered this period)
- Highest and weighted-average study drug dose in the entire treatment period.
- IMTD
- IMD

Weighted-average dose is computed with weighting on the amount of time exposed to each study drug dose according to the drug log eCRF.

5.3.2 Compliance with study treatment

Compliance will be assessed as described in the study protocol. Compliance below 80% or above 120% will be reported as a protocol deviation based on the monitoring methodology.

5.3.3 Study treatment discontinuation

Patients who completed study [see Section 5.4] and who did not discontinue study drug prematurely are considered study treatment completers.

Premature discontinuations of study drug are recorded on a specific page in the eCRF. The primary reason for study drug discontinuation will be collected as well.

5.3.4 Study treatment adjustments or interruptions

The study treatment log eCRF page collects start date, end date, dose and frequency of study treatment. The reason for study drug adjustments, interruptions or discontinuations is recorded for the termination of each dose record.

5.4 Study discontinuation

Patients completing study will be derived from the SDTM DS data panel.

For patients who prematurely discontinue the study, the associated reason(s) is entered in the eCRF.

5.5 Efficacy variables

Actigraphy assessments will be generated for each day by Actigraph® algorithms and included in the SDTM datasets.

Scores from the PAH-SYMPACT® electronic patient reported outcomes (ePRO) diary will be included in the SDTM datasets. Domain scores will be generated by analysis programming.

Results from the 6MWT and WHO FC are entered by the investigator in the eCRF. N-terminal pro b-type natriuretic peptide (NT-proBNP) is assessed by the central lab. These will be transferred in the SDTM

5.5.1 Primary efficacy variables

5.5.1.1 Actigraphy DLPA endpoints in protocol

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

The primary efficacy variables, as defined in the protocol, include the change from baseline to Week 24 or EOT in actigraphy-assessed DLPA as measured by:

- Daily time spent (minutes) in non-sedentary activity (≥ 100 counts per minute).
- Percentage of daily time spent in non-sedentary activity (≥ 100 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 protocol defined thresholds based on the Freedson's the uniaxial hip worn accelerometer counts [Freedson 1998]. This study is using the wrist worn accelerometer at the non-dominant wrist, and a conversion factors are applied according to Table 1.

The measurement of physical activity (PA) may not fully measure hand movement-related PA, which could capture relevant information for QoL and mental health. Therefore, PA

measured at the wrist may differ from PA measured at the hip, despite existing conversion rules.

On the other hand, no conversion is required for the Koster's non-sedentary activity threshold, which is measured by a triaxial ActiGraph accelerometer worn at the non-dominant wrist.

Since TRACE is an exploratory study, time spent in non-sedentary activity will be analyzed using both Freedson and Koster algorithms.

In addition, a recent communication by Bellerophon Therapeutics on the positive outcome of a Phase 2b clinical trial using the endpoint of daily time spent in MVPA led to the decision to analyze MVPA in TRACE. In response to FDA feedback for another Actelion studies, i.e., AC-055H301 (RUBATO) and macitentan 75 mg in CTEPH (NDA 204410), the volume of non-sedentary activity, including number of steps, has also been added to the TRACE CSR SAP and will be analyzed [see details in Section 4.3.2].

The full details of the actigraphy additional DLPA endpoints are provided in the next section and summarized in table 3.

5.5.1.2 DLPA actigraphy endpoints

The following primary efficacy endpoints are used in this SAP.

1) Change from Baseline to Week 24/EOT in daily time spent in non-sedentary activities (minutes) – Freedson

   Definition: Daily time spent in non-sedentary activities (minutes) defined as ≥ 100 y-axis hip counts per minute (i.e., ≥ 187 y-axis wrist converted counts per minute). This is the sum of time spent (minutes) in light, moderate, vigorous, and very vigorous activities during wear and awake time per day.

2) Change from Baseline to Week 24/EOT in daily time spent in MVPA (minutes) – Freedson

   Definition: Daily time spent in MVPA (minutes) defined as ≥ 1952 y-axis hip counts per minute (i.e., ≥ 2603 y-axis wrist converted counts per minute). This is the sum of time spent (minutes) in moderate, vigorous, and very vigorous activities during wear and awake time per day.

3) Change from Baseline to Week 24/EOT in daily time spent non-sedentary activities (minutes) – Koster

Definition: Daily time spent in non-sedentary activities (minutes) defined as ≥ 1853 triaxial vector magnitude (VM) counts per minute. This is the sum of time spent (minutes) in non-sedentary activities during wear and awake time per day.

4) Change from Baseline to Week 24/EOT in percentage of daily time spent in non-sedentary activities – Freedson

   Definition: Percentage of daily time spent in non-sedentary activities (≥ 187 y-axis wrist converted counts per minute) defined as the sum of time spent (minutes) in light, moderate, vigorous, and very vigorous activities during wear and awake time divided by daily total wear and awake minutes.

5) Change from Baseline to Week 24/EOT in percentage of daily time spent in MVPA – Freedson

   Definition: Percentage of daily time spent in non-sedentary activities (≥ 2603 y-axis wrist converted counts per minute) defined as the sum of time spent (minutes) in moderate, vigorous, and very vigorous activities during wear and awake time divided by daily total wear and awake minutes.

6) Change from Baseline to Week 24/EOT in percentage of daily time spent in non-sedentary activities – Koster

   Definition: Percentage of daily time spent in non-sedentary activities (≥ 1853 triaxial VM counts per minute) defined as the sum of time spent (minutes) in non-sedentary activities during wear and awake time divided by daily total wear and awake minutes.

7) Change from Baseline to Week 24/EOT in volume of total activity (counts/minutes)

   Definition: Volume of total activity counts/minute defined as sum of triaxial vector magnitude counts during wear and awake time per day divided by daily total wear and awake minutes.

8) Change from Baseline to Week 24/EOT in volume of non-sedentary activity during awake time (counts, computed over one day [24 hours]) – Koster

   Definition: Volume of non-sedentary activities defined as sum of counts above the sedentary threshold (≥ 1853 triaxial VM counts per minute) during wear and awake time per day.

9) Change from Baseline to Week 24/EOT in volume of non-sedentary activity during awake time, per awake time (counts/minute, computed over one day [24 hours]) – Koster

   Definition: Volume of non-sedentary activities defined as sum of counts above the sedentary (≥ 1853 triaxial VM counts per minute) during wear and awake time per day divided by daily total wear and awake minutes.

10) Change from Baseline to Week 24/EOT in number of steps during awake time (step counts, computed over one day [24 hours])

    Definition: Number of steps during wear and awake time per day.

11) Change from Baseline to Week 24/EOT in number of steps during awake time, per awake time (step counts/minute, computed over one day [24 hours])

    Definition: Number of steps during wear and awake time per day divided by daily total wear and awake minutes.

The detailed analysis methods of the DLPA actigraphy endpoints are specified in Section 10.6. The derivation of DLPA actigraphy endpoints from the ActiGraph daily summary parameters are specified in Section 11.8

5.5.1.3 Sleep endpoints

The following sleep variables are used:

12) Change from Baseline to Week 24/EOT in TST (minutes)

13) Change from Baseline to Week 24/EOT in WASO (minutes)

14) Change from Baseline to Week 24/EOT in number of awakenings (counts)

15) Change from Baseline to Week 24/EOT in sleep efficiency (percentage)

Sleep endpoints will be provided on a by-episode basis by the Actigraphy provider. To capture the impact of the study medication on night-time sleep endpoints, only sleep episodes beginning between 7:00 pm and 6:59 am and ending no later than 11:59 am will be used as valid episodes at night for the definition of the sleep endpoints.

Some patients may have multiple sleep episodes in a night. For TST, WASO, and number of awakenings, the assessments of eligible episodes will be summed up for each night. The sleep efficiency endpoint will be assigned to an analysis night as described before. Sleep efficiency will be summarized on a sleep episode basis but will not be summed up for a nightly value.

This algorithm is, however, exploratory, as no known literature data currently provide robust information about the derivation of actigraphy sleep-related endpoints. This might lead to be biased results, and this will be further discussed in the final report. The sleep endpoints may show less association with the secondary endpoints. All sleep endpoints will be only summarized descriptively.

The summary of primary endpoints shows in the Table 3.

Table 3 Summary of primary endpoints

Primary endpoints (in SAP)	Unit	Algorithm	DLPA/ Sleep	Rationale	Endpoints (as per written in protocol)
1) Change from Baseline to Week 24/EOT in daily time spent in non-sedentary activities	min	Freedson 1998	DLPA	As per protocol	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)
2) Change from Baseline to Week 24/EOT in daily time spent in MVPA	min	Freedson 1998	DLPA	Same as Bellerophon	n.a.
3) Change from Baseline to Week 24/EOT in daily time spent non-sedentary activities	min	Koster 2016	DLPA	More reliable	n.a.
4) Change from Baseline to Week 24/EOT in percentage of daily time spent in non-sedentary activities	%	Freedson 1998	DLPA	As per protocol	Change from baseline to Week 24/EOT in actigraphy-assessed DLPA as measured by percentage of daily time spent in non-sedentary activity (≥ 100 activity counts per minute)
5) Change from Baseline to Week 24/EOT in percentage of daily time spent in MVPA	%	Freedson 1998	DLPA	same as Bellerophon	n.a.
6) Change from Baseline to Week 24/EOT in percentage of daily time spent in non-sedentary activities	%	Koster 2016	DLPA	more reliable	n.a.
7) Change from Baseline to Week 24/EOT in volume of total activity counts/minutes	counts / min	n.a.	DLPA	As per protocol	Change from baseline to Week 24/EOT in actigraphy-assessed DLPA as measured by total DLPA in counts/min
8) Change from Baseline to Week 24/EOT in volume of non-sedentary activity during awake time (counts, computed over one day [24 hours])	counts	Koster 2016	DLPA	FDA feedback in other studies	n.a.
9) Change from Baseline to Week 24/EOT in volume of non-sedentary activity during awake time, per awake time (counts/minutes, computed over one day [24 hours])	counts / min	Koster 2016	DLPA	FDA feedback in other studies	n.a.

Primary endpoints (in SAP)	Unit	Algorithm	DLPA/ Sleep	Rationale	Endpoints (as per written in protocol)
10) Change from Baseline to Week 24/EOT in number of steps during awake time (counts, computed over one day [24 hours])	steps	n.a.	DLPA	FDA feedback in other studies	n.a.
11) Change from Baseline to Week 24/EOT in number of steps during awake time, per awake time (counts/minutes, computed over one day [24 hours])	steps/ min	n.a.	DLPA	FDA feedback in other studies	n.a.
12) Change from Baseline to Week 24/EOT in TST	min	n.a.	sleep	As per protocol	Change from baseline to Week 24/EOT in actigraphy-assessed DLPA as measured by Sleep: TST (minutes), WASO (minutes), number of awakenings, efficiency (percentage)
13) Change from Baseline to Week 24/EOT in WASO	min	n.a.	sleep	As per protocol	
14) Change from Baseline to Week 24/EOT in number of awakenings	counts	n.a.	sleep	As per protocol	
15) Change from Baseline to Week 24/EOT in sleep efficiency	%	n.a.	sleep	As per protocol	

DLPA = daily life physical activity; EOT = End-of-Treatment; MVPA = n.a. = not applicable; TST = total sleep time; WASO = wake after sleep onset; Moderate to Vigorous Physical Activity (Freedson '98).

5.5.2 Secondary efficacy variables

5.5.2.1 PAH-SYMPACT® domain scores:

Change from baseline to Week 24 or EOT in:

- Cardiovascular symptom domain score
- Cardiopulmonary symptom domain score
- Physical impact domain score
- Cognitive/emotional impact domain score

5.5.2.2 WHO functional class

Shift from baseline to Week 24 or EOT in WHO FC.

5.5.2.3 6-minute walk test

Change from baseline to Week 24 or EOT for following variables:

- 6-minute walk distance (6MWD)
- Borg dyspnea index during 6MWT

5.5.2.4 N-terminal pro b-type natriuretic peptide (NT-pro BNP)

Change from baseline to Week 24 or end of treatment for NT-proBNP.

The detailed analysis methods for secondary efficacy variables are specified in Section 10.7.

5.5.3 Variables used for correlation analyses

These variables will consist of:

- Actigraphy DLPA variables and other secondary efficacy endpoints. For this CSR, correlations between secondary efficacy endpoints and DLPA actigraphy endpoints are planned (detailed analysis methods are specified in Section 10.8). A more detailed analysis of associations (i.e., anchoring variables) will be described in a separate document.

5.6 Safety variables

Safety endpoints as stipulated in the protocol comprise:

- Treatment-emergent AEs and treatment-emergent SAEs up to 3 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 3 days after study treatment discontinuation.
- SAEs and Deaths up to 30 days after study treatment discontinuation.

5.6.1 Adverse events

All AEs will be coded using the MedDRA dictionary in its latest version at time of database closure.

5.6.1.1 Treatment-emergent adverse events

Treatment-emergent AEs are defined as those AEs occurring from study treatment start up to 3 days after end of study treatment.

5.6.1.2 Frequency of treatment-emergent adverse events

Treatment-emergent AEs reported more than once within a patient, are counted in the frequency table once.

5.6.1.3 Intensity of treatment-emergent adverse events

For treatment-emergent AEs reported more than once within a patient, the worst intensity is considered.

5.6.1.4 Relationship of treatment-emergent adverse events

Relationship to study treatment is defined as 'related' or 'not related' as judged by the investigator. For treatment-emergent AEs reported more than once within a patient, the worst relationship is considered (i.e., related). Adverse events with missing relationship are considered in any analysis as related.

5.6.2 Deaths

The primary reason for death is reported on a specific eCRF page. SAEs leading to death are marked on the AE eCRF form.

5.6.3 Serious adverse events

SAEs are all AEs that have been marked as serious by the investigator or where the seriousness assessment is missing in the database.

5.6.4 Adverse events leading to discontinuation of study treatment

AEs where action taken with study treatment is "Drug withdrawn" are analyzed as AEs leading to discontinuation of study treatment.

5.6.5 Other significant adverse events

5.6.5.1 AEs of special interest (AESIs) based on the selexipag risk management plan (RMP)

The adverse events of special interest (AESIs) will be retrieved using preferred terms (PTs) or standardized MedDRA queries (SMQs). The latest available categories are described in Appendix 3. A list of MedDRA terms for the identified/potential risks of selexipag will be provided by Actelion drug safety for each update of the RMP and/or MedDRA version.

5.6.5.2 AEs typical of prostanoid treatments

The AEs typical of prostanoid treatments will be retrieved from the database by selecting the following MedDRA PTs:

Arthralgia, Diarrhoea, Dizziness, Flushing, Headache, Pain in jaw, Musculoskeletal pain, Myalgia, Nausea, Pain in extremity, Temporomandibular joint syndrome, Vomiting.

5.6.5.3 Non-serious AEs

For the disclosure of the results to EudraCT and ClinicalTrials.gov, non-serious AEs are defined.

A non-serious AE is any AE with the question "Serious?" answered "No" by the investigator.

5.6.6 Vital signs and body weight

Body weight, SBP, DBP, and pulse rate are collected at each study visit at the site. BMI will be derived at each visit.

Treatment-emergent vital signs and body weight assessments up to 3 days after study treatment discontinuation will be analyzed.

5.6.7 Electrocardiogram

Not applicable.

5.6.8 Laboratory

A central laboratory is used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data are loaded into the clinical database. However, in exceptional or emergency cases local laboratory results (with the corresponding variables and normal ranges) may also be used in parallel and entered into the clinical database via dedicated eCRF pages.

In the analysis only central laboratory values will be used. If a central laboratory value is not available but a local laboratory assessment is available, the local laboratory value will be used to account for lost or non-analyzable samples in the central laboratory.

A basic panel for hematology and biochemistry will be evaluated:

Hematology: White blood cell count (WBC), Hemoglobin, Hematocrit, Red blood cell count (RBC), Platelet count, Differential (% and absolute).

Clinical chemistry: Sodium, Potassium, Chloride, Bicarbonate, BUN/Urea, Creatinine, Glucose, Calcium, Phosphorus, Magnesium, Total Protein, Albumin, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, AST (SGOT), ALT (SGPT), GGT, Alkaline Phosphatase, LDH

Treatment emergent laboratory assessments up to 3 days after study treatment discontinuation will be analyzed. Additional laboratory variables collected will be listed but not used in summaries.

Marked abnormal laboratory data are determined according to Document OTH-000005 [see Section 1.1].

The detailed analysis methods for safety variables are specified in Section 10.9.

5.7 Quality of life variables

Quality of life endpoints are efficacy endpoints and described in Section 5.5.

6 DEFINITION OF PROTOCOL DEVIATIONS

Protocol deviations (PDs) are determined by the study team in a blinded fashion. Major PDs leading to exclusions from analysis sets are determined and databased prior to unblinding to the study.

PDs are described in the PD list referred in Section 1.1.

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Screened analysis set

This analysis set will include all patients who were screened and received a patient number.

7.1.2 Full analysis set

The Full Analysis Set (FAS) will include all patients randomly assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible, analyses on the FAS will use the following rules:

- Patients will be 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 will be included (e.g., including assessments after study treatment discontinuation).

7.1.3 Per-protocol analysis set

The Per-Protocol Analysis Set (PPS) will comprise 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 sufficient exposure to treatment, availability of measurements and absence of major PDs that have an impact on the treatment effect. Patients will be excluded from the PPS if they meet at least one of the following criteria:

- Patient is not randomized or received treatment different from the treatment it was randomized to
- Patient prematurely discontinued treatment
- Patient was not consented properly or violated inclusion or exclusion criteria: Protocol deviation identifier (PDID) 101, 202 – 247
- Patient had insufficient treatment compliance: PDID 405
- Forbidden concomitant medication used: PDID 501, 511, 521

Subjects will be evaluated according to the study drug to which they were assigned to.

Patients will be evaluated according to the study drug to which they were assigned to.

Exclusions from the PPS will be identified from the protocol deviation SDTM panel for all PDs which have PDIDs. All other exclusions from the PPS will be programmed.

7.1.4 Safety analysis set

The Safety Analysis Set (SAF) will include all patients who received at least one dose of study treatment. The analysis will be based on the actual treatment received. If a patient

received both selexipag and placebo treatments in error, the patient will be analyzed in the selexipag arm.

7.1.5 Other analysis sets

Not applicable.

7.2 Usage of the analysis sets

The usage of the analysis sets is summarized in Table 4 below.

Table 4 Overview of the different analysis sets and their usage

Analyses/Data Displays	Screened analysis set	Full analysis set	Safety analysis set	Per protocol set
Patient disposition	✓			
Demographics		✓		✓
Baseline characteristics		✓		✓
Medical history		✓		
Previous and concomitant therapies		✓		
Treatment exposure			✓	✓
Efficacy: Primary endpoint		✓		✓
Efficacy: Secondary endpoints		✓		✓
Efficacy: Exploratory endpoints		✓		
Safety endpoints			✓	
All other patient listings[1]	✓			

[1] Unless indicated otherwise

8 DEFINITION OF SUBGROUPS

Subgroup analyses will be conducted based on relevant demographics or baseline disease characteristics.

The following subgroup variables will be used for the analyses:

- Region [see Section 4.1.3]
  - UK
  - non-UK
- Sex
  - Male
  - Female
- WHO functional class at baseline
  - I/II
  - III/IV
- Age at screening
  - <65 years
  - ≥65 years

Other subgroup variables, in accordance with the AC065A302 (GRIPHON) trial, will be used for the analyses if at least 15 patients are contained in each subgroup category:

- Baseline concomitant PAH specific therapy
  - No PAH specific therapy
  - Endothelin receptor antagonist (ERA) monotherapy
  - Phosphodiesterase-5 inhibitor (PDE5i) or soluble guanylate cyclase (sGC) stimulator monotherapy
  - ERA and PDE5i (or sGC stimulator) combination therapy
    NOTE: Concomitant use of PDE5is and sGC stimulators is not allowed.
- Race
  - Caucasian
  - Asian
  - Black
  - Other/Unknown
- PAH etiology at baseline (group 1)
  - Idiopathic
  - Associated with connective tissue disease
  - Others (i.e. heritable, drug- or toxin-induced, associated with HIV infection, and associated with congenital heart disease with simple systemic-to-pulmonary shunt ≥ 1 year after surgical repair)
- PAH etiology at baseline (group 2)
  - Associated with connective tissue disease

– Others (i.e. Idiopathic, heritable, drug- or toxin-induced, associated with HIV infection, and associated with congenital heart disease with simple systemic-to-pulmonary shunt ≥ 1 year after surgical repair).

9 GENERAL STATISTICAL METHODOLOGY

All statistical analyses are run by the CRO Datamap GmbH, Freiburg, Germany using SAS 9.4 or higher on a SUN Solaris system.

The analyses of the study data will comprise univariate and multivariate exploratory analyses to generate hypotheses on new endpoints. Thus, no difference will be made between primary and secondary efficacy analyses.

The methodology below describes the minimum set of planned analyses; the list may be expanded depending on data driven findings.

9.1 Statistical models for continuous data

9.1.1 Analysis of covariance

An analysis of covariance model (ANCOVA) including terms for treatment as factor, and baseline value as covariate will be fitted to all continuous primary and secondary endpoints (except of sleep parameters). The differences in least square means between selexipag and placebo, corresponding 2-sided 95% confidence interval (CI), and p-value will be provided.

SAS code as shown below will be used; for *analysis_dataset*, *treatment, response, and baseline* the corresponding dataset and variable names will be inserted.

The stratification factor (i.e., North America versus Europe/Rest of the World) was planned to be added to the above ANCOVA model as per protocol. However, only a very few North Americans were enrolled in this study. In the preceding AC-065A302/GRIPHON study, regional differences were only observed in the distribution of PAH-specific medication at baseline. Therefore, the stratification factor of North America versus Europe/Rest of the world will be removed from the ANCOVA model.

```
PROC MIXED DATA=analysis_dataset;
CLASS treatment ;
MODEL response = treatment  baseline;
LSMEANS treatment /PDIFF CL ALPHA=0.05;
RUN;
```

9.1.2 Mixed model analysis with repeated measures

A mixed model analysis of repeated measures (MMRM) will be fitted to continuous DLPA related primary endpoints. The model will include terms for baseline value, treatment, visit,

and treatment by visit interaction as covariates. Visits will be repeated measures within patients with an unstructured covariance matrix. Fixed effect tests will be computed using the Kenward-Rogers method to determine the degrees of freedom of the denominator. An unstructured variance-covariance matrix will be used for observations clustered by patient. In case of convergence problems, alternative variance-covariance structures will be evaluated in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate patient random effect.

The overall and by-visit differences in least square means between selexipag and placebo, corresponding 2-sided 95% CI, and p-value will be provided using appropriate contrasts.

SAS code as shown below will be used; for *analysis_dataset*, *visit, patient id, treatment, response and baseline*, the corresponding dataset and variable names will be inserted.

```
PROC MIXED DATA=analysis_dataset;
CLASS treatment visit subj_id;
MODEL response = treatment visit treatment*visit baseline /DDFM=KR;
REPEATED visit / SUBJECT=patient_id TYPE=UN;
LSMEANS treatment /cl;
LSMEANS treatment*visit /cl
RUN;
```

10 STATISTICAL ANALYSES

10.1 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% CIs 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.

10.2 General rules for data presentations

10.2.1 General guidelines for table contents

Summary statistics for continuous variables will include number of non-missing observations (n), mean, standard deviation (SD), median, 1st and 3rd quartiles, minimum, and maximum. For discrete variables, the number of patients in the respective category and the relative frequency (percentage) will be shown. Missing values will be shown as a separate category and included in the computation of percentages.

All summaries are presented by treatment arm in the respective population. The order of the treatment arms will be ‘Selexipag’ and then ‘Placebo’. Patient disposition, demographics, baseline characteristics and exposure summaries will additionally be

presented with a 'Total' treatment column to convey a summary of the total population assessed in this study.

10.2.2 General guidelines for table layout and formats

The guidelines in the Biostatistics Standards Document of the Actelion Standardization Project Standard outputs are followed.

Summaries of continuous variables will be shown with the same precision (i.e., number of decimals) as the original value for minimum and maximum; precision +1 (i.e., one more decimal than source data) for mean, median, and quartiles; precision +2 for standard deviation. P-values are presented with 4 decimals. P-values smaller than 0.0001 are presented as '<0.0001'.

Individual patient listings are ordered by treatment arm (in order "Selexipag", "Placebo" and "Not randomized") country, center, patient number, and assessment date.

10.3 Display of patient disposition, protocol deviations and analysis sets

10.3.1 Patient disposition

The following information will be presented on the screened analysis set:

- Number of patients screened for inclusion and reason for screen failures
- Number of patients randomized
- Number of patients treated with study treatment
- Number of patients who completed and discontinued study treatment
- Reasons for study treatment discontinuation
- Number of patients who completed and discontinued the study
- Reasons for study discontinuation.

Reasons for screen failure will be listed on the screened set. Treatment completion status and study completion status (i.e., completed or withdrawn together with reason for withdrawal) as well as randomization information will be listed on the FAS.

10.3.2 Protocol deviations

The number and percentage of patients with PDs (PDs leading to exclusion from the PPS, important PDs, and all PDs) will be summarized as defined in Section 6 on the FAS.

All PDs will be listed on the screened set. PDs leading to exclusion from an analysis set will be flagged.

10.3.3 Analysis sets

The number and percentage of patients included in each analysis set will be summarized on the FAS. The reasons for exclusion from any analysis set will be presented.

10.4 Analyses of patient characteristics

Patient characteristics will be analyzed on the FAS and PPS.

10.4.1 Demographics

Baseline demographics as described in Section 5.2.1 will be summarized with descriptive statistics. Age will be analyzed as a continuous variable and as a categorical variable with categories < 18 (if applicable), 18–64, ≥ 65 years.

The summary will be conducted for all patients and by subgroup. All demographics will be listed.

10.4.2 Baseline disease characteristics

Baseline disease characteristics as described in Section 5.2.2 will be summarized descriptively. The time since the initial PAH diagnosis will be summarized in months as a continuous variable.

The baseline concomitant PAH specific treatment will be summarized by the number of medications taken concomitant to baseline (one, two, ≥ three and the categories shown in Table 2.

Results from the most recent RHC will be converted into standard units, if necessary. The time since the most recent RHC will be summarized in months.

Baseline 6MWD (in meters) and the Borg dyspnea score will be summarized as a continuous variable.

Baseline concomitant therapies and PAH specific therapies will be summarized [see Section 10.4.4].

The summary will be conducted for all patients and by subgroup. All baseline disease characteristics will be listed.

10.4.3 Medical history

Previous diseases will be summarized by MedDRA system organ class (SOC) and PT. SOCs and PTs within SOCs will be ordered by descending frequency. A second summary will be prepared on the PT level only.

Study concomitant diseases will be analyzed in the same way as previous diseases.

10.4.4 Previous baseline concomitant and concomitant therapies

For study reporting purposes, all previous and study-concomitant therapies are reported in the patient listings.

Previous therapies, baseline concomitant therapies and concomitant therapies initiated during the study treatment period are summarized by therapeutic organ class and preferred term. A second summary is prepared by preferred term only.

Previous, baseline concomitant and concomitant PAH specific therapies initiated during the study treatment period are summarized by mode of action category [see Table 2] and WHODRUG preferred term.

10.5 Analysis of study treatment exposure and compliance

All exposure analyses are conducted on the SAF and PPS.

10.5.1 Exposure

The definition of the variables analyzed for exposure is given in Section 5.3.1.

Exposure to study treatment will be summarized in days. Furthermore, the number and percentage of patients being exposed at least 1, 14, 28, 56, 84, 112, 140, and 168 days will be given in categories.

Exposure will be summarized graphically as inverse cumulative distribution function.

The maximum and weighted-average selexipag dose will be summarized as a continuous variable for:

- The titration period
- The maintenance period (for patients entering the maintenance period)
- Entire treatment period.

The study drug IMTD and IMD will be summarized with number and percentage of patients by each dose category (0 mcg, 200–400 mcg b.i.d., 600–1000 mcg b.i.d., and 1200–1400 mcg b.i.d.) and each dose level. Study drugs' IMTD and IMD will also be summarized as continuous variable.

Exposure analyses will be presented by subgroup.

10.5.2 Compliance with study treatment

Deviations from treatment compliance will be summarized as PD [see Section 10.3.2].

10.5.3 Study treatment discontinuation

Study treatment discontinuation is summarized within the patient disposition [see Section 10.3.1].

10.5.4 Study treatment adjustments and interruptions

The study drug administration log (start and end dates, dose) will be listed. Reasons for study drug interruptions and discontinuations as entered in the eCRF will be given.

10.6 Analysis of the primary efficacy variables

This is an exploratory study. All actigraphy variable analyses are listed as primary efficacy variables in Section 5.5.1.

All actigraphy variables collected between informed consent and end-of-study (EOS) will be presented in patient listings.

10.6.1 Hypothesis and statistical model

There will be no confirmatory hypotheses testing in the analysis of this trial.

All statistical testing procedures used, if any, will provide exploratory p-values. CIs will be two-sided at the 95% level. No adjustment for multiplicity will be made.

10.6.2 Main analysis

10.6.2.1 Analysis of DLPA actigraphy endpoints

All actigraphy DLPA endpoints (i.e., the endpoints 1 to 11 in Section 5.5.1.2) are treated as continuous variables. These are expected to be approximately normally distributed. Should there be relevant deviations from normality, appropriate transformation of the data (e.g., log transformation, inverse logit, …) may be applied before analysis.

All actigraphy endpoints will be aggregated into 14-day windows for analysis. Baseline will be the average of the last 14 days prior to first dose of study drug (Day −1 to Day −14); post baseline assessments will be aggregated in 14-day intervals as shown in Table 5.

Likewise, the last 14 days prior to the last dose of study treatment will be used for determination of the EOT value. All subjects will have the EOT value, unless subject withdrew within a week of treatment start or no actigraphy data available after the study Day 7 [see Section 10.6.3 for handling of missing data].

If enough valid data have been collected in a time window at an analysis visit [see Section 10.6.3 for handling of missing data], the average of the values assessed within the time window will be used as analysis value.

Actigraphy data collection will be independent of actual study visits, e.g., Week 16 data will be always be averages between Day 99 and 112, regardless of when the actual study visit took place.

Table 5 Actigraphy assessment time windows

Analysis Visit	Start Day	End Day
Baseline	−14	−1
Week 2	1	14
Week 4	15	28
Week 6	29	42
Week 8	43	56
Week 10	57	70
Week 12	71	84
Week 14	85	98
Week 16	99	112
Week 18	113	126
Week 20	127	140
Week 22	141	154
Week 24	155	168
EOT[1]	Last study treatment − 14 days*	Last study treatment − 1 day*

[1] EOT value will be computed out of the last two weeks prior to last study treatment, regardless if the last study treatment date was before, at, or after Day 168.
* EOT will have a valid value. If EOT value based on the period (EOT-14, EOT-1) is missing (not valid), the EOT period will be rolled back by one day, i.e., (EOT-15, EOT -2), (EOT-16, EOT-3), and so on until a non-missing (valid) value is available. The period can be rolled back until (1, 14).
EOT = End-of-Treatment.

The actigraphy DLPA endpoints will be summarized descriptively for each analysis visit together with the respective absolute and percentage change from baseline. The number of patients with a missing of actigraphy assessments (include invalid assessments) at any given visit will be presented as well.

The main analysis, change from baseline to Week 24/EOT in the DLPA actigraphy endpoints, will be analyzed using an ANCOVA model with treatment baseline value of the actigraphy parameter as covariates. Least squares means of treatment group differences of the actigraphy DLPA endpoints as well as the corresponding 95% confidence intervals will be provided. Imputation rules are described in Section 10.6.3. The ANCOVA model will be applied on the imputed Week 24/EOT values.

The main analysis will be conducted on the FAS.

The sensitivity/supportive analyses and subgroup analyses will be conducted [see details in Section 10.6.4 and Section 10.6.4.3].

10.6.2.2 Analysis of Sleep endpoints

The sleep parameters (i.e., the endpoints 12 to 15 in Section 5.5.1.3) are provided on a by-episode basis by Actigraph, before being derived for the analysis.

For the derivation of sleep endpoints, the by-episode data will be transformed for each night using the following algorithm: All sleep episodes starting between 7:00 pm and 6:59 am (next day) and ending no later than 11:59 am (next day) will be used. The data for each actigraphy sleep endpoint will be aggregated to form one single night assessment, with an allocated analysis visit day corresponding to the day of evening starting that night, e.g., all eligible assessments starting from Day X − 1 at 7:00 pm up to Day X 06:59 am will be summed up and assigned to the night of Day X − 1. Then, baseline and post-baseline night assessments will be aggregated into bi-weekly windows for analysis as described in Table 5.

For the sleep efficiency, when patients have multiple episodes in a night, the time between episodes could be considered as a long awakening period, and it would introduce low efficiency per night. However, the device used for this study does not enable patients to register their bed-in and bed-out times. The above algorithm may not be reflecting patients' real sleep patterns. In this SAP, sleep efficiency will be summarized on a sleep episode basis, and will not be summed up for a nightly value. Consequently, sleep efficiency per analysis visit will be based on all (possibly more than 14) episodes during the 14 nights.

For the sleep endpoints, no ANCOVA model, sensitivity/supportive analysis, nor subgroup analyses will be performed.

10.6.3 Handling of missing data

Actigraphy variables will be considered valid (non-missing) for a specific time window if the data are available for at least 7 complete days (consecutive or not) within that time window of assessment.

For DLPA actigraphy endpoints, a complete day is defined as a record of at least 7 awake hours of data. If less than 7 complete days are available, the value of the time window will be set to missing.

For sleep endpoints, at least one valid episode of any length must be present for each night to obtain a valid assessment. Sleep endpoints must be present for at least 7 nights (consecutive or not) within each 14-day window; otherwise the value of the time window will be set to missing.

In case of premature discontinuation of study drug, the average of the last non-missing 14-day window prior to the last dose of study treatment will always be used as an EOT value. If the EOT value corresponding to the period (EOT-14, EOT-1) is missing (not valid), the EOT period will be rolled back by one day, i.e., (EOT-15, EOT-2), (EOT-16, EOT-3), until a non-missing (valid) value is available. This corresponds to a last observation carried forward (LOCF) up to Week 24/EOT approach. If no post-baseline actigraphy data have been collected for at least 7 days over a 14-day time window, no EOT value will be computed, and the post-baseline value will be set as missing.

10.6.4 Supportive/sensitivity analyses

Supportive and sensitivity analyses will be performed for DLPA actigraphy endpoints.

10.6.4.1 Supportive analyses

For the endpoints based on Freedson algorithm (i.e., the endpoints 1, 2, 4, and 5 in Section 5.5.1.2), the daily time spent and percentage of daily time spent will be also summarized descriptively according to activity categories "sedentary", "light", "moderate", "vigorous", and "very vigorous" on the FAS.

10.6.4.2 Sensitivity analyses

All ANCOVA analyses on the primary efficacy actigraphy endpoints for DLPA will be repeated on the PPS.

The additional following sensitivity analyses will be performed on the FAS: all actigraphy DLPA endpoints will additionally be analyzed using a MMRM model with baseline value, treatment, analysis visit, and interaction between treatment and analysis visit as covariates. Treatment group differences contrasts will be computed overall and for each analysis visit (i.e., Week 2, Week 4, Week6, …, Week 24) and displayed with the respective 95% CIs. No imputed values will be used for the MMRM analysis. These sensitivity analyses assume missing at random.

In case of multiple or notably unbalanced discontinuations or missing data (i.e., 15% more missing in one group as compared to the other), additional methods such as multiple imputation models may be explored to further assess the impact of missing values on the main actigraphy DLPA endpoints (e.g., top 3 DLPA actigraphy parameters shown stronger correlation with 6MWD). These potential sensitivity analyses assuming not missing at random will be performed using Tipping Point Analyses.

10.6.4.3 Subgroup analyses

Subgroup analyses for the change from baseline to Week 24/EOT for all DLPA actigraphy endpoints (the endpoints 1 to 11) will be conducted on the subgroup variables listed in Section 8, based on the FAS. The analyses are conducted to assess consistency of the overall treatment effect across subgroup variables.

The above main ANCOVA analyses will be repeated with each subgroup variables tested separately. Treatment group differences of least squares means as well as the corresponding 95% confidence intervals within each subgroup level will be presented.

The treatment-by-subgroup interaction p-value will be estimated using a separate model including treatment, baseline actigraphy value, subgroup, and treatment-by-subgroup interaction term(s). Interactions with p-value < 0.01 will be investigated further to determine the nature of the interaction (quantitative of qualitative) and the association with other subgroups.

Results are presented in a summary table and in forest plot for each endpoint. The forest plot will display the "overall" treatment effect, based on the main ANCOVA analysis, as a reference line. Least squares means of the treatment group differences, the corresponding 95% confidence intervals, and the numbers of patients in the subgroup levels will be presented in the forest plot.

10.6.4.4 Compliance of DLPA endpoints

DLPA endpoints are required at least 7 complete days (i.e. at least 7 awake hours per day) within 14-day time window as per protocol. The different cut-off of awake hours and/or number of complete days will be affected on results, if there are some imbalance between the treatment groups. The number of valid days (at least 7 hours of wear and awake hours per day), and daily wear and awake time (hours) in the 14day time-window as defined in Table 5 will be summarized descriptively. For the Week 2 – Week 24, if a day of DLPA recodes are missing before the EOT, the day will be handled as zero awake and wear hour.

10.7 In case of notable unbalanced in compliance of DLPA, sensitivity analysis will be performed as mentioned in Section 10.6.4.2. In addition, the impact of weekday and weekend activities may be explored on a few of actigraphy DLPA endpoints (e.g., top 3 DLPA actigraphy parameters shown stronger difference between treatment arms). Analysis of the secondary efficacy variables

All analyses of secondary efficacy variables will be based on the FAS.

All secondary efficacy variables collected between informed consent and EOS will be presented in patient listings.

10.7.1 Secondary endpoints

10.7.1.1 Hypothesis and statistical model

There will be no confirmatory hypotheses testing in the analysis of this trial.

All statistical testing procedures used, if any, will provide exploratory p-values. CIs will be two-sided at the 95% level. No adjustment for multiplicity will be made.

10.7.1.2 Statistical analysis

PAH-SYMPACT® domain scores

The four PAH-SYMPACT® questionnaire domain scores will be derived using the scoring algorithm described in Section 11.9.

The four domain scores, cardiovascular symptom domain score, cardiopulmonary symptom domain score, physical impact domain score, and cognitive/emotional impact domain score, will be derived for three seven-day periods corresponding to the following study visits: Baseline period, Week 16, and Week 24/EOT [see details in Appendix 2].

The four domain scores at baseline, absolute value and absolute change from baseline at Week 16 and Week 24/EOT by treatment group will be summarized using the descriptive statistics. For the change from baseline to Week 24/EOT, treatment group difference will be estimated using the ANCOVA model as described in Section 9.1.1.

WHO functional class

The WHO functional class will be analyzed descriptively by presenting a summary at each study visit and a shift table from baseline to Week 16 and Week 24/EOT. Additionally, the shift from baseline to the highest and lowest post-baseline value will be presented. The analysis will be presented for all patients and by subgroup.

6MWD and Borg dyspnea index

The 6MWD and Borg dyspnea index (as a continuous variable) at baseline, and absolute value and change from baseline at Week 16 and Week 24/EOT will be analyzed using the descriptive methods. For the change from baseline to Week 24/EOT, treatment group differences will be estimated using the ANCOVA model as described in Section 9.1.1.

NT-proBNP

NT-proBNP will be analyzed descriptively as described for the primary efficacy endpoints in Section 10.6.2.

For the ANCOVA model, NT-proBNP will be log-transformed as NT-proBNP assessments follow more closely a log-normal distribution.

The change of log-transformed NT-proBNP values from baseline to Week 24/EOT will be analyzed using an ANCOVA model with treatment and log transformed baseline NT-proBNP and other covariates. Least squares means of the treatment group differences as well as the corresponding 95% CIs will be back transformed before being presented, thus providing a geometric mean ratio between the treatment groups.

10.7.1.3 Handling of missing data

Handling of missing data for the derivation of PAH-SYMPACT® scores is described in Section 11.9.

To account for missed assessments and unscheduled visits, all assessments of secondary efficacy data (except PAH SYMPACT scores) will be assigned to the most appropriate timepoint using Table 8 in Section 11.6.

For all secondary efficacy endpoints, a LOCF approach will be used: If the Week 24 domain score is not available, the last post-baseline value is carried forward. The ANCOVA models will be performed using on the imputed data using LOCF.

10.7.1.4 Supportive/sensitivity analyses

The analyses of secondary endpoints described above will be repeated on the PPS.

10.7.1.5 Subgroup analyses

Descriptive analyses of secondary efficacy variables will be conducted by subgroup as described in Section 8.

10.8 Correlation Analysis

The association between actigraphy DLPA endpoints (the endpoints 1 to 11 in Section 5.5.1.2) and the other efficacy endpoints (PAH-SYMPACT® domain scores, 6MWD, NT-proBNP, WHO-FC) will be evaluated. Scatter plots of change from baseline to EOT of the actigraphy DLPA endpoints (at Week 24/EOT) [see Section 5.5.1.2] versus change from baseline of the other efficacy endpoints ate Week 24/EOT with the corresponding Pearson correlation coefficients will be presented. In addition, the Pearson correlation coefficient for the changes from baseline to Week16 and Week 24, and absolute value at Baseline, Week 16, and Week 24 will be tabulated. NT-proBNP data will be log transformed for the correlation analysis.

Table 6 Time windows for analysis of association between DLPA endpoints and secondary endpoints

Analysis Visit	Target Day	6MWD, WHO FC, NT-proBNP, and PAH-SYMPACT®			Actigraphy assessment period	
		Lower limit of study day	Upper limit of study day	Assessment date*	Start date	End date
Baseline	1	Latest assessment before or at Day 1		X_{BL}	−14	−1
Week 16	113	2	141	X_{16}	$X_{16}-14$	$X_{16}-1$
Week 24	169	142	EOS	X_{24}	$X_{24}-14$	$X_{24}-1$
EOT	EOT (Last assessment)	2	EOS	X_{EoT}	$X_{EoT}-14$	$X_{EoT}-1$

* For PAH-SYMPACT®, the date of the 7th day will be used to determine the actigraphy assessment period.
6MWD = 6-minute walk distance; EOT = end of treatment; NT-proBNP = N-terminal pro b-type natriuretic peptide; PAH-SYMPACT® = Pulmonary Arterial Hypertension Symptoms and Impact questionnaire; WHO FC = World Health Organization functional class. EOS = end of study (Secondary endpoints are measured a few days after EOT)

10.9 Analysis of safety variables

The safety endpoints in this study are defined in Section 5.6.

All safety analyses will be based on the SAF except where stated otherwise.

10.9.1 Adverse events

All AEs captured from signature of informed consent up to EOS are reported in the patient listings.

Treatment-emergent AEs, including SAEs, will be summarized for each treatment groups by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary SOC, and having each individual AE (at the PT level). The display will be ordered by descending order of incidence of SOCs and PTs within SOCs in the (double-blind) selexipag group.

The analysis will be repeated by presenting for each treatment group, the number and percentage of patients having any AE, and having each individual AE (at the PT level). The display will be ordered in descending order of incidence of PTs.

Furthermore, treatment-emergent AEs, including SAEs, will be summarized by severity, SOC, and PT. For each patient, SOC, and PT the highest severity will analyzed.

All AEs collected in the eCRF, i.e., AEs starting between signature of informed consent and the day prior to the first dose of study treatment, will be listed. The listing will be based on the screened patients set and will also include AEs of patients who were screened but not randomized. Some patients will start using commercial selexipag after end of study treatment. AEs occurring during the commercial selexipag will be indicated in the listings.

10.9.2 Deaths, other serious adverse events

10.9.2.1 Death

All study deaths will be listed together with the primary reason for study death as entered on the specific eCRF page will be listed.

A second listing will be prepared displaying all AEs leading to death as entered in the AE eCRF page.

10.9.2.2 Serious adverse events

Treatment emergent SAEs (+3 days after treatment discontinuation) will be summarized by presenting a summary by SOC and PT and by PT as described in Section 10.9.1.

A separate summary will be presented for SAEs occurring between first day of study drug and up to +30 days after treatment discontinuation.

SAEs prior to first dose of study treatment and occurring later than 30 days after the end of treatment will be presented in listings if entered in the clinical database.

A separate listing will be prepared presenting all SAEs, regardless of relationship to study drug.

10.9.2.3 Adverse events leading to study treatment discontinuations

AEs leading to study treatment discontinuation will be summarized by SOC and PT and by PT as described in Section 10.9.1.

A separate listing will be prepared for all AEs leading to study treatment discontinuation.

10.9.2.4 Other significant adverse events

AEs related to study drug

Treatment-emergent AEs which are related to study drug as judged by the investigator will be summarized by SOC and PT.

AESIs based on the selexipag Risk Management Plan (RMP)

Treatment-emergent AESIs based on the selexipag RMP will be summarized by treatment group for each AESI category, including:

- the number and percentage of patients having an AESI
- the relative risk compared to placebo (only on the safety set)
- patients with at least one AESI leading to discontinuation of study drug, serious AESIs, fatal AESIs
- Number and annualized rate of recurrent events
- Observed PTs
- Maximum severity

AEs typical of prostanoid treatments

AEs typical of prostanoid treatments [see Section 5.6.5.2] will be summarized for each treatment group, by presenting the number and percentage of patients having any AE, and having each individual AE (at the PT level). The display will be ordered in descending order of incidence of PTs of the selexipag treatment arm.

10.9.2.5 Summaries of AEs for Clinical Trial data disclosure

For the disclosure of the results to EudraCT and ClinicalTrials, treatment-emergent (S)AEs will be summarized for each treatment group, displaying counts and percentages of patients with at least one treatment-emergent event plus the number of events (counted exactly the number of times they occurred also within a patient) by SOC and individual PT. The summary table is presented in descending order according to the incidence in the selexipag treatment group (i.e., SOC and individual preferred term within each SOC with the highest number of occurrences appears first). Equal frequency of different individual preferred terms is sorted in alphabetical order of the individual PT.

The following summaries will be prepared according to the guidelines stated above:

- Summary of treatment emergent SAEs

- Summary of treatment emergent SAEs judged to be treatment related by the investigator
- Summary of treatment emergent SAEs with fatal outcome
- Summary of treatment emergent SAEs with fatal outcome judged to be treatment related by the investigator
- Summary of treatment emergent non-serious AEs with an incidence of 5% or higher in any treatment group

10.9.3 Laboratory tests

Laboratory data, regardless if from scheduled or unscheduled visits will be used for analysis. Central lab values will be used for analysis; local lab values will be used only if no central lab value is available for the laboratory test [see Section 5.6.8].

The laboratory data will be assigned to the most appropriate analysis time point using time windows as described in Table 9 in Section 11.6.

10.9.3.1 Laboratory tests over time

Hematology and biochemistry values will be summarized by treatment group and by visit in their respective SI unit together with the respective changes from baseline for Week 16 and Week 24. Only treatment emergent (i.e., up to 3 days after last dose of study treatment) laboratory tests will be used for summaries.

All laboratory values will be listed.

10.9.3.2 Marked laboratory abnormalities

Actelion internal guidelines (OTH-000005) 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 their correspondence to scheduled or unscheduled assessments.

Table 7 Definition of marked laboratory abnormalities

Parameter (SI unit)	LL Marked	LLL Alert	HH Marked	HHH Alert
Hemoglobin (g/L) baseline within ULN baseline above ULN	 <100 <100	 <80 <80	 >20 above ULN >20 above baseline	 >40 above ULN >40 above baseline
Hematocrit (L/L) males females	 <0.32 <0.28	 <0.20 <0.20	 >0.60 >0.55	 >0.65 >0.65
Platelets (10E9/L)	<75	<50	>600	>999
Leucocytes (10E9/L)	<3	<2	>20	>100
Neutrophils (10E9/L)	<1.5	<1.0	-	-
Eosinophils (10E9/L)	-	-	>5	-
Lymphocytes (10E9/L)	<0.8	<0.5	>4	>20
ALT/SGPT	-	-	>3 ULN	>5 ULN
AST/SGOT	-	-	>3 ULN	>5 ULN
GGT	-	-	>2.5 ULN	>5 ULN
Alkaline Phosphatase	-	-	>2.5 ULN	>5 ULN
Total Bilirubin	-	-	>2 ULN	>5 ULN
Creatinine baseline within ULN baseline above ULN	 - -	- - -	 >1.5 ULN >1.5 baseline	 >3 ULN >3 baseline
Glucose (mmol/L)	<3	<2.2	>8.9	>13.9
Calcium (mmol/L)	<2	<1.75	>2.9	>3.1
Sodium (mmol/L)	-	<130	>150	>155
Potassium (mmol/L)	<3.2	<3	>5.5	>6
Magnesium (mmol/L)	<0.5	<0.4	-	>1.23
Phosphate (mmol/L)	<0.8	<0.6	-	-
Urate (µmol/L)	-	-	>590	>720
Albumin (g/dL)	<30	<20	-	-
Creatinine Clearance (mL/min)	<60	<30	-	-
BUN	-	-	>2.5 ULN	>5 ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyltransferase; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamate-pyruvate transaminase; ULN = upper limit of normal.

The number and percentage of patients with treatment-emergent (i.e., up to 3 days after last dose) post-baseline laboratory abnormalities will be tabulated by treatment group.

10.9.3.3 Marked laboratory hepatic abnormalities

The incidence of the following important treatment-emergent (i.e., up to 3 days after last dose) laboratory hepatic abnormality will be tabulated by treatment group:

- ALT ≥ 3×ULN
- AST ≥ 3×ULN
- ALT or AST ≥ 3×ULN
- ALT or AST ≥ 3×ULN + < 5×ULN
- ALT or AST ≥ 5×ULN + < 8×ULN
- ALT or AST ≥ 8×ULN
- ALT or AST ≥ 3×ULN + total bilirubin > 2×ULN (at the same time as ALT or AST ≥ 3×ULN)

10.9.4 Vital signs and body weight

10.9.4.1 Vital signs and body weight over time

Weight, BMI, pulse rate, systolic and diastolic blood pressure will be summarized together with the respective changes from baseline for all scheduled study visits.

Treatment emergent vital signs assessments within 3 days of the last dose of study treatment will be used for summaries. All data, regardless if from scheduled or unscheduled visits are used; vital signs assessments will be assigned to the most appropriate analysis time point using time windows as described in Table 9 in Section 11.6.

10.9.4.2 Marked blood pressure abnormalities

The number and percentage of patients with treatment-emergent (i.e., within 3 days of last dose) post-baseline blood pressure abnormalities will be tabulated by treatment group. All blood pressure assessments are taken into account, regardless of association to scheduled or unscheduled visits.

The incidence of the following notable treatment emergent blood pressure values post baseline will be tabulated:

- SBP < 90 mmHg
- DBP < 50 mmHg
- Decrease of > 40 mmHg in SBP from baseline
- Decrease of > 20 mmHg in DBP from baseline
- All four notable criteria fulfilled.

10.10 Analysis of quality of life variables

The analysis of the PAH-SYMPACT® questionnaire is described as a secondary endpoint [see Section 10.7.1.2].

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Study treatment start- and end date

Study treatment is selexipag or placebo. Thus, the date of the first dose of selexipag/placebo is study treatment start date and the date of the last dose of selexipag/placebo is the study treatment end date (EOT date).

11.2 Treatment emergent assessments or events

Treatment emergent assessments or events are assessments made or events experienced between the study treatment start date and 3 days after the last dose of study treatment.

11.3 Study days

Study days are relative to the date of first study treatment. The date of first study treatment is Day 1. There is no Day 0, i.e., the Day before Day 1 is Day −1.

11.4 Duration in months

Number of months between two study dates will be computed by counting the number of days between the two dates (including the dates) and dividing be 30.4.; i.e.,

Duration (months) = (End date - Start date + 1) / 30.4

11.5 Baseline definition

The last value prior to or on the date of the first dose of study treatment is considered baseline. All assessments made on the first day of study drug intake (Day 1) are considered as prior to study drug intake for the determination of baseline.

For patients randomized but not treated with study treatment, the last value prior to or on the date of randomization is considered baseline. All assessments made on the day of randomization are considered as prior to randomization for the determination of baseline.

Note that AEs starting on Day 1 are considered as on study treatment unless ‘Onset prior to first dose of study treatment’ on the eCRF page is ticked ‘Yes’.

For PAH-SYMPACT®, the baseline definition is shown in Appendix 2.

11.6 Visit windows

To account for unscheduled visits, missed or postponed assessments all study site based assessments will be mapped to the most appropriate visit. The assessment closest to the target date will be used. If two assessments are equally close to the target date, the earlier assessment will be used.

Table 8 Time windows for efficacy assessments, at the exception of actigraphy

Analysis Visit	Target Day	Lower limit of study day	Upper limit of study day
Baseline	1	Latest assessment before or at Day 1	
Week 16	113	2	141
Week 24	169	142	EOS
EOT	EOT (Last assessment)	2	EOS

EOT = end of treatment. EOS = end-of-study (Some of secondary endpoints are measured a few days after EOT)

Table 9 Time windows for treatment-emergent safety assessments

Analysis Visit	Target Day	Lower limit of study day	Upper limit of study day
Baseline	1	Latest assessment before or at Day 1	
Week 16	113	2	141
Week 24	169	142	EOT + 3 days

EOT = end-of-treatment.

11.7 Handling of selexipag/placebo dose titrations between morning and evening dose

In some patients, dose changes (up- or down-titration) may be conducted over the day in the b.i.d. regimen of selexipag/placebo, i.e., the dose taken in the evening is higher or lower than the dose taken in the morning. In the eCRF, overlapping intervals of dosages are recorded in such a case: The end date of the old regimen is recorded with the same date as the start date of the new regimen. To account for the actual daily dose the following handling convention will be used:

1. The end date of the old dose regimen will be reduced by one day
2. The start date of the new dose regimen will be increased by one day
3. A record with the average dose will be created for the day of dose change, i.e. the overlapping date

An example from the selexipag/placebo dosage log is shown in Table 10.

Table 10 Illustrative example for handling of selexipag/placebo dose titrations over day

Dose start	Dose end	Regimen	Total daily dose
As recorded in the eCRF			
01Sep2016	16Sep2016	200 mcg b.i.d.	400 mcg
16Sep2016	30Sep2016	400 mcg b.i.d.	800 mcg
Handling rule for analysis			
01Sep2016	15Sep2016	200 mcg b.i.d.	400 mcg
16Sep2016	16Sep2016	---	600 mcg
17Sep2016	30Sep2016	400 mcg b.i.d.	800 mcg

b.i.d. = twice daily; eCRF = electronic case report form.

11.8 Derivation of DLPA actigraphy endpoints

All activity counts collected during the time of patient was awake and wore the Actigraphy device will be provided on a daily summary basis by the Actigraphy provider (ActiGraph).

The following derivations will be used for each DLPA actigraphy endpoint. The variable names are based on "Data Transfer Agreement (ActiGraph), Revision N, dated 21 November 2019" with horizontal database structure. The names will be changed in SDTM according to SDTM's vertical data structure.

1) For daily time spent in non-sedentary activities (minutes – based on Freedson algorithm), the values of 'WFAwakeCutpointsLight', 'WFAwakeCutpointsModerate', 'WFAwakeCutpointsVigorous', 'WFAwakeCutpointsVeryVigorous' will be summed up.

2) For daily time spent in MVPA (minutes – based on Freedson algorithm), the values of 'WFAwakeCutpointsModerate', 'WFAwakeCutpointsVigorous', 'WFAwakeCutpointsVeryVigorous' will be summed up.

3) For total daily time spent in non-sedentary activity (minutes – based on Koster algorithm), the value of 'WFAwakeKosterNonSedentary' will be used.

4) For percentage of daily time spent in non-sedentary activity (% – based on Freedson algorithm), the sum of 'WFAwakeCutpointsLight', 'WFAwakeCutpointsModerate', 'WFAwakeCutpointsVigorous', 'WFAwakeCutpointsVeryVigorous' will be divided by 'WearAwakeMinutes'.

5) For percentage of daily time spent in MVPA (% – based on Freedson algorithm), the sum of 'WFAwakeCutpointsModerate', 'WFAwakeCutpointsVigorous', 'WFAwakeCutpointsVeryVigorous' will be divided by 'WearAwakeMinutes'.

6) For percentage of time spent in in non-sedentary activity (% – based on Koster algorithm), the value of 'WFAwakeKosterNonSedentary' will be divided by 'WearAwakeMinutes'.

7) For total DLPA (counts / minute), the values of 'WFAwakeTotalVectorMagnitude' will be divided by 'WearAwakeMinutes'.

8) For volume of non-sedentary activity during awake time (counts – based on Koster algorithm), the values of 'WFATotalVectorMagnitude-K-NS' will be used.

9) For volume of non-sedentary activity during awake time, per awake time (counts – based on Koster algorithm), the values of 'WFATotalVectorMagnitude-K-NS' divided by 'WearAwakeMinutes'.

10) For number of steps during wake time (steps), variable 'WearFilteredAwakeTotalSteps' will be used.

11) For number of steps during awake, per awake minute (steps / min), the value of 'WearFilteredAwakeTotalSteps' divided by 'WearAwakeMinutes'.

The Actigraph device must be worn for at least seven awake hours on any given day in order to provide a valid DLPA assessment, i.e., the mean DLPA count will only be computed if wear and awake time is greater or equal $7 \times 60 = 420$ minutes. If the wear time is below 420 minutes on a specific day, the DLPA count will be set to missing [see also Section 10.6.3].

11.9 Scoring the PAH-SYMPACT® questionnaire

The PAH-SYMPACT® is composed of two parts: the Symptoms part (11 items), which is assessed daily for seven days; and the Impacts part (11 items), which is assessed once at the end of a seven-day period.

11.9.1 Symptoms

Each item is scored daily on a Likert Scale ranging from 0 (best) to 4 (worst). The average score across the seven-day period for each symptom item will be computed, if at least 4 days of valid answers are available. Otherwise the item score will be set to missing.

Then the weekly averages will be aggregated into domain scores by taking the arithmetic mean of the average weekly item scores of all symptom items belonging to a domain [see Table 11].

Domains with an even number of item scores will be scored if at least half of the item scores are non-missing; domains with an odd number of item scores will be scored if at least half of the item scores plus one item are non-missing. Otherwise the domain score will be left as missing.

Table 11 Symptom scores domains

Domain	Item
Cardiopulmonary Symptoms Domain	How would you rate your shortness of breath?
	How would you rate your fatigue?
	How would you rate your lack of energy?
	How would you rate the swelling in your ankles or legs?
	How would you rate the swelling in your stomach area?
	How would you rate your cough?
Cardiovascular Symptoms Domain	How would you rate your heart palpitations (heart fluttering)?
	How would you rate your rapid heartbeat?
	How would you rate your chest pain?
	How would you rate your chest tightness?
	How would you rate your lightheadedness?

11.9.2 Impact

Each item is scored once for the past seven days on a Likert Scale ranging from 0 (best) to 4 (worst).

Domain scores will be computed by taking the arithmetic mean of the item scores of all symptom items belonging to a domain [see Table 12].

Domains with an even number of item scores will be scored if at least half of the item scores are non-missing; domains with an odd number of item scores will be scored if at least half of the item scores plus one item are non-missing. Otherwise the domain score will be left at missing.

Table 12 Impact scores domains

Domain	Item
Physical Impacts Domain	Were you able to walk slowly on a flat surface?
	Were you able to walk quickly on a flat surface?
	Were you able to walk uphill?
	Were you able to carry things, such as bags or baskets?
	Were you able to do light indoor household chores such as preparing food, cleaning surfaces, or tidying up?
	Were you able to wash or dress yourself?
	How much did you need help from others?
Cognitive/Emotional Impacts Domain	Were you able to think clearly?
	How sad did you feel?
	How worried did you feel?
	How frustrated did you feel?

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

Missing and incomplete date and time fields should be avoided as far as possible. However, in some cases complete dates cannot be obtained with reasonable effort. In those cases, imputation of incomplete dates or incomplete date parts will be employed.

Dates are split in 3 parts: year, month, and day. Year is the top level, month is medium level, and day is low level. Missing date parts will be imputed into acceptable non-missing values in a way depending on the type of date to be replaced.

In the following sections, ‘lower limit’ and ‘upper limit’ refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. The earliest and the latest of different dates refer to the first or last date, respectively, when ordered in sequence.

12.1 Imputation of previous/concomitant medication and therapy dates

12.1.1 Previous/concomitant medication and therapy start date

Date is incomplete	Date is missing
Lower limit except when: Not tagged as ongoing at start of study treatment AND Medication stop date not collected or with the upper limit after the study treatment start AND The treatment start day falls in the range of possible dates. In which case it is the ***study treatment start day***	No replacement, the medication is considered to have started before the study

12.1.2 Previous/concomitant medication and therapy end date

Date is incomplete	Date is missing
Upper limit except when: Medication start is before study treatment start or missing AND Upper limit is after the study treatment start AND Not tagged as ongoing at start of study treatment AND Not tagged as ongoing at last visit In which case it is ***1 day before study drug start***	No replacement (considered ongoing)

12.2 Imputation of AE start and end dates

12.2.1 AE start date

Date is incomplete	Date is missing
If the end date of the AE is not before the start of study treatment, and if the study drug start falls in the range of possible dates, it is the study drug start date. In all the other cases, it is the lower limit	The earlier of the end date of the AE and the start of study drug.

12.2.2 AE end date

Date is incomplete	Date is missing
The upper limit	No replacement, the AE is considered as ongoing in the analysis

12.3 Imputation of other date fields

12.3.1 Date of PAH diagnosis

Date is incomplete	Date is missing
Day missing: 15th of the month Day and month missing: 30th of June If the resulting date is later than the date of screening visit date and the lower limit is not later than the screening visit date, then the date is substituted with the date of screening visit.	No replacement

13 REFERENCES

[Cole 1992] Cole RJ1, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. Sleep. 1992;15:461-469.

[Freedson 1998] Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc. 1998;30:777-781.

[Koster 2016] Koster A, Shiroma EJ, Caserotti P, Matthews CE, Chen KY, Glynn NW, Harris TB. Comparison of sedentary estimates between activPAL and hip and wrist-worn ActiGraph. Med Sci Sports Exerc. 2016;48:1514-1522.

[Matthews 2008] Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. Am J Epidemiol. 2008;167:875-881.

[Nathan 2019] Nathan SD, Flaherty K, Glassberg MK, Raghu G, Swigris J, Alvarez R, et al. Actigraphy as a clinically meaningful endpoint to detect change after treatment with iNO (30 mcg/kg-IBW/hr) in patients at risk of Pulmonary Hypertension associated with Pulmonary Fibrosis. 13th Annual Pulmonary Vascular Research Institute World Congress on Pulmonary Vascular Disease, January 31 to February 3, 2019, Barcelona, Spain.

[Sehgal 2019] Sehgal S, Chowdhury A, Rabih F, Gadre A, Park MM, Li M, et al. STep-count using an Accelerometer for Monitoring PAH—STAMP Study. Lung. 2019;197:501-508.

[Tremblay 2010] Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. Appl Physiol Nutr Metab. 2010;35(6):725-740.

[Troiano 2008] Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M: Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008;40:181-188.

[Tudor-Locke 2014] Tudor-Locke C, Barreira TV, Schuna JM Jr., Mire EF, Katzmarzyk PT. Fully automated waist-worn accelerometer algorithm for detecting children's sleep-period time separate from 24-h physical activity or sedentary behaviors. Appl Physiol Nutr Metab. 2014;39:53-57.

14 APPENDICES

Appendix 1 Protocol synopsis and study visit assessment schedule

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].

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

	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 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)

	○ Total DLPA in counts/min ○ 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: ○ 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) **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]. Secondary/exploratory analyses: 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. Safety analysis: All safety analyses will be performed on the Safety Set using descriptive statistics. Sample size: 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 13 Study periods, visits at study site and assessments

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.

Appendix 2 Baseline for PAH-SYMPACT® Scores

1) Check the existence of "impact" assessment before study treatment start.

2) If **yes,** check the latest assessment date on "impact" questionnaire items before study treatment start. This assessment date will be handled as an anchor date for the baseline ePRO (=Day -X_i).

If **no**, check the latest assessment date on "symptom" questionnaire items before study treatment start. This date will be handled as an anchor date for the baseline ePRO (=Day -X_s).

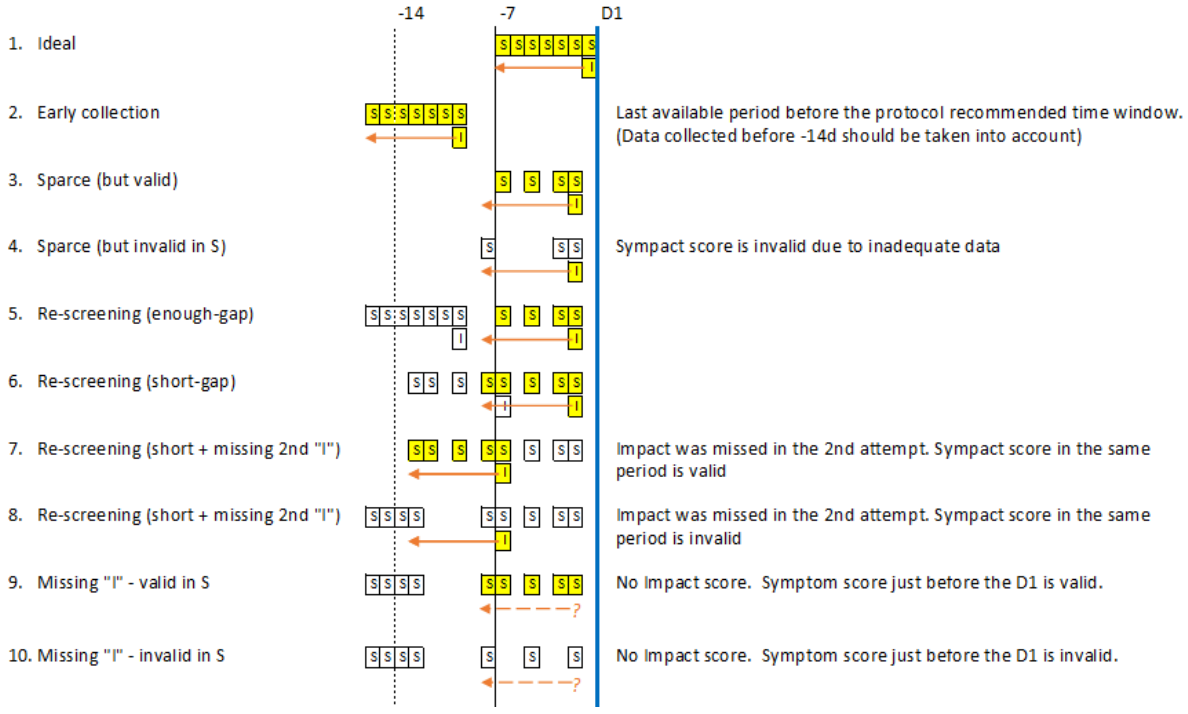
3) The anchor date will be considered as the last date of the baseline ePRO.

Therefore, the baseline ePRO assessment period will be:

a. [Day - (X_i + 6), Day - X_i] for symptoms, with corresponding impacts assessment at Day - X_i

b. [Day - (X_s + 6), Day - X_s] for symptoms, without corresponding impacts assessment.

Figure 2 Possible patterns of PAH-SYMPACT® period at baseline



The cells with "S" and "I" indicate the "symptom" and "impact" assessments in the baseline ePRO. The orange arrows indicate the 7 days baseline ePRO period. The yellow cells indicate the valid scores at baseline, these values will be used for calculation of baseline domain scores. White cells will not be used for domain score. These values will be used for listing only.

In the post-baseline ePRO periods, some patients might have more than 7 days assessments in a period. If so, the same concept will be applied. i.e., check the existence of “impact” assessment in a period, and set up the 7 days assessment period based on the last impact assessment date, or last symptom assessment date (when impact is missing). The patients are allowed to enter the assessment until the next day 02.00 AM.

Appendix 3 Adverse events of special interest

The following adverse events of special interest will be used for selexipag. These are based on the important identified and potential risks in the latest Risk Management Plan and on-going discussion with Pharmacovigilance Risk Assessment Committee.

AE Special Interest Category
Anaemia
Bleeding events
Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
Hyperthyroidism
Hypotension
Light-dependent non-melanoma skin malignancies
Major adverse cardiovascular events (MACE)
Medication errors
Ophthalmological effects associated to retinal vascular system
Pregnancy
Pulmonary venoocclusive disease associated with pulmonary oedema
Renal function impairment / acute renal failure
Thrombocytopenia
Prostacyclin associated reactions*

*Prostacyclin associated reactions will be summarized separate from other AESIs

Adverse events of special interest are defined per the file available in the ICE folder:

root/Selexipag/Selexipag_across_indications/AC-065_Standard/BIOS/val/val_meddra/doc_aesi

Appendix 4 Document history

Version	Effective Date	Reason
1.0	10-Jan-2017	New
2.0	16-Dec-2019	New findings on ActiGraph primary endpoints, and modifications are necessary [details in Section 4]
3.0	27-Feb-2020	Based on the FDA type C meeting: - Section 10.6.4.4. Compliance of DLPA endpoint was newly added. In line with the (standard) documents or latest dictionaries: - Section 1.1. Updated study documents - Section 5.3.1.1. IMTD detailed definition in line with RMP. - Section 5.3.1.1. IMTD, CYP2C8 category was modified according to the latest version of Standardized Drug Groupings Others, e.g. fine tuning, precisions etc.: - Section 4.1.3. Subgroup analyses. Add explanation of UK vs non-UK will not considered in ANCOVA. - Section 5.5.1.2. DLPA endpoint 7) was modified from "total DLPA" to "volume of total activity". Because it's the volume and link with endpoints 8) and 9). - Section 5.5.1.3. conflicting information was deleted. - Section 7.2. Table 4. Delete the PPS on exploratory endpoints. - Section 8. Subgroup of PAH etiology. Updated as per clinical interest and reasonable numbers in each group during the blinded data review. - Section 9.1.1. Remaining "region" was deleted (Other than this section, region has already been deleted in the SAP version 2.0) - Section 10.6.2.1. Duplicated sentence was deleted. Sentence for listing was deleted (due to the size of data, listing is not meaningful). - Section 10.8. Table 6. "EOT (Last assessment)" and footnote were added for giving the precise definitions. - Section 11.6. Table 8 added the EOT in line with Table 6. - Section 11.8. Derivation of Actigraphy endpoints 8) and 9) were updated based on the blinded data received from the vendor (ActeGraph). - Appendix 2. Assessment window was extended based on blinded data. - Appendix 3. Off label use was deleted, because it's not expected in clinical trial.