STATISTICAL ANALYSIS PLAN FOR CSR

VERSION 3

THE EFFICACY AND SAFETY OF INITIAL TRIPLE VERSUS INITIAL DUAL ORAL COMBINATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED PULMONARY ARTERIAL HYPERTENSION: A MULTI-CENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3B STUDY (TRITON)

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	Six-minute walk distance
ADaM	Analysis data model
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
b.i.d.	Twice daily
bpm	Beats per minute
CEC	Clinical Events Committee
CI	Cardiac index
CO	Cardiac output
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
CTD	Connective tissue disease
ECG	Electrocardiography
eCRF	Electronic case report form
EOS	End-of-study
EOMOP	End of main observation period
EOT	End-of-treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full analysis set
FC	Functional class
FDA	Food and Drug Administration
GMR	Geometric mean ratio
IA	Interim analysis

IDMC	Independent data monitoring committee
IMD	Individual maintenance dose
IMTD	individual maximum tolerated dose
ISAC	Independent statistical analysis center
KM	Kaplan-Meier
LOCF	Last observation carried forward
LVEDP	Left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MI	Multiple imputation
MMRM	Mixed model repeated measures analysis
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
MTD	Maximum tolerated dose
NT-proBNP	N-terminal pro B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PD	Protocol deviation
PDE	Phosphodiesterase
PH	Pulmonary hypertension
PPS	Per-protocol analysis set
PVR	Pulmonary vascular resistance
PT	Preferred Term
RHC	Right heart catheterization
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation

SEM	Standard error of the mean
SMQ	Standardized MedDRA Queries
SOC	System organ class
SI	Système international d'unités
TC	Teleconference
TPR	Total pulmonary resistance
ULN	Upper limit of the normal range
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the derivations of efficacy and safety endpoints, the analyses and the presentation of analysis results and data for the clinical study report (CSR) of study AC-065A308 (TRITON).

This SAP also describes the blinded outputs provided on a regular basis for independent data monitoring committee (IDMC) open session meetings (see IDMC charter). Those blinded outputs for IDMC are a subset of CSR outputs and are flagged accordingly in list of outputs provided in Section 13.

The unblinded analyses for IDMC closed sessions (including futility interim analysis) are performed by the Independent Statistical Analysis Center (ISAC) according to ISAC's own analysis plan. The study team remains blinded. The ISAC is responsible for the content of these unblinded analyses for the closed reports provided to the IDMC (see IDMC charter).

Electronic Case Report Form (eCRF) is used for all subjects. Laboratory samples are processed through a central laboratory and the results are loaded electronically into the clinical database. All data are converted into study data tabulation model datasets and are provided by data management. 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-065A308, version 6, dated 4 December 2018 [D-18.392]
- eCRF, version 004, dated 3 May 2017
- Case report form (CRF) completion guidelines, version 3.0, dated 9 January 2018
- Data management plan, final version 3, dated 5 January 2018
- Protocol deviation code list, version 4, dated 10 May 2019
- Definition of Marked Abnormalities in Laboratory Data (OTH-000005), Version 09, dated 1 November 2017

Any change to any of those documents affecting the biostatistics deliverables will require this SAP and related documents to be updated accordingly.

2 STUDY DESIGN AND FLOW

For a detailed description refer to the study protocol [D-18.392].

2.1 Study design

This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3b, efficacy and safety study comparing a triple oral regimen

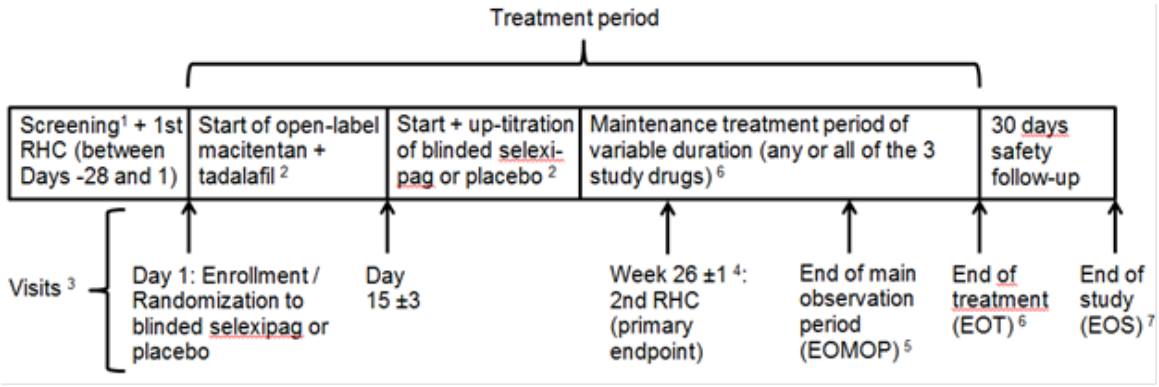
(macitentan, tadalafil, selexipag) with a dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with pulmonary arterial hypertension (PAH).

This study uses a group sequential design, with one interim analysis for futility (non-binding) planned when approximately one third of the subjects have completed their Week 26 pulmonary vascular resistance (PVR) assessment (primary endpoint) or have prematurely discontinued the study. The interim analysis will be performed by the ISAC for the IDMC who will provide Actelion with their recommendation to either continue or prematurely terminate the study for futility.

Approximately 238 subjects are randomized in a 1:1 ratio to the two treatment groups (approximately 119 subjects per group), stratified by region (North America versus rest of the world) and WHO functional class (FC) at baseline (I/II versus III/IV). The study is conducted at approximately 75 sites in approximately 20 countries. Randomization proceeds until the required number of subjects has been reached. It is competitive across participating sites. Actelion may replace sites with no subject enrollment.

The study periods at the subject level are summarized in Figure 1. Figure 2 illustrates the planned duration of the study and the duration of the subjects' participation in the study.

Figure 1 Study periods (subject level)



[1] Signed written informed consent is required prior to any study-mandated procedure (RHC data obtained at the study site before informed consent signature but within 28 days prior to Day 1 are acceptable).

[2] Study treatment initiation scheme: See study protocol [D-18.392]

[3] For simplification, most visits between Day 1 and EOMOP (as defined below) are not displayed.

[4] If double-blind treatment (Selexipag/Placebo) is discontinued before Week 26: The Week 26 assessments should be done either at Week 26 or before start of rescue therapy (prostacyclin, prostacyclin analog, or prostacyclin receptor agonist), whichever is first.

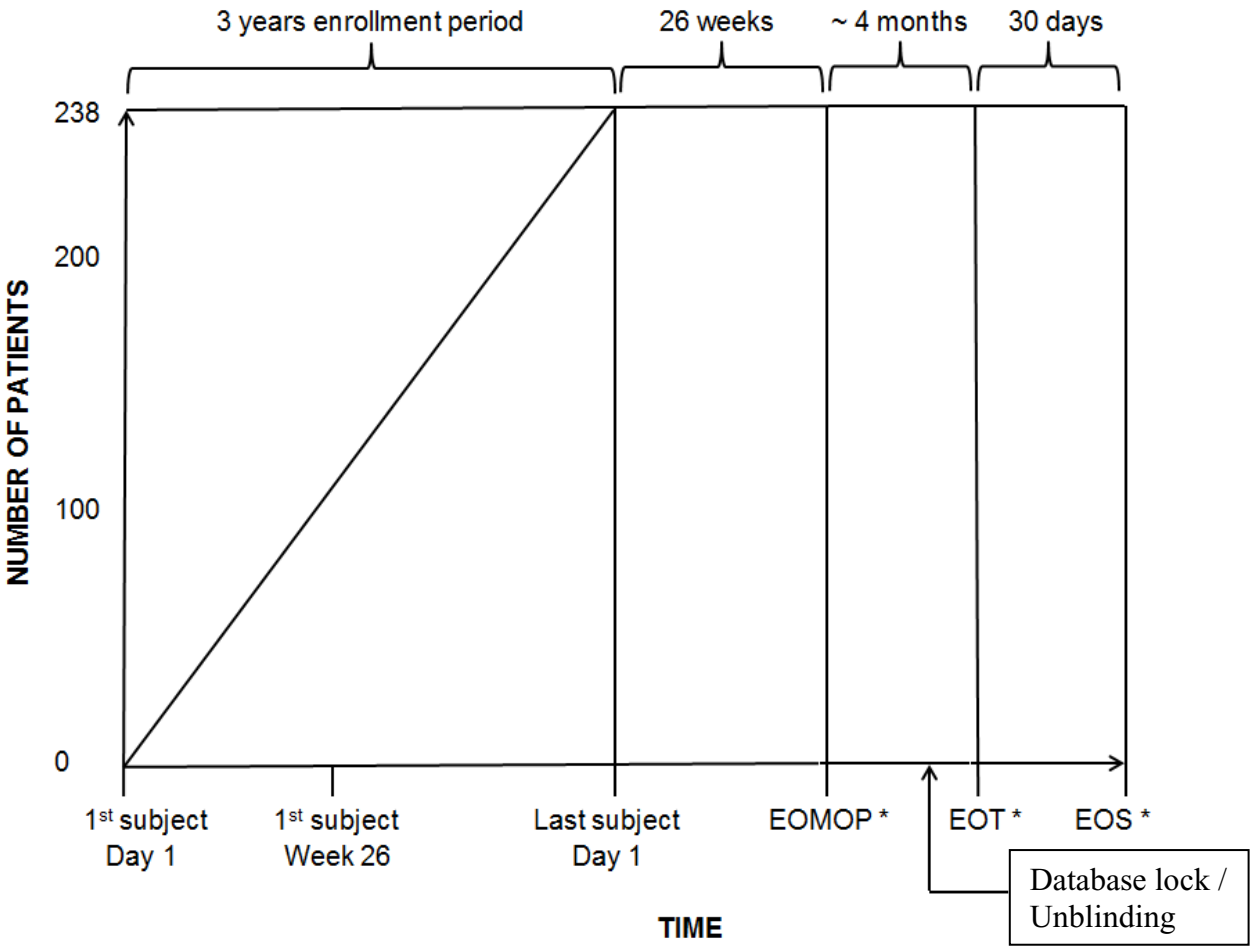
[5] The EOMOP is the data cutoff for the main efficacy and safety analyses, followed by data cleaning and unblinding of the treatment group allocation. The EOMOP visit is planned 26 ± 1 week after enrollment of the last subject. This timepoint is announced by Actelion approximately 6 months in advance. The EOMOP visit is not required if within ± 2 weeks of a patient's Week 26 visit or Month 12, 18, 24, 30, etc. visit.

[6] All 3 study treatments are provided until the EOT visit, which is planned approximately 4 months after the EOMOP visit. In order to allow sufficient time for the investigator to arrange any post-study therapy, Actelion announces EOT approximately 10 months in advance, and unblind the treatment group allocation (Selexipag or Placebo) approximately 1 month prior to EOT. In the event of premature discontinuation of all 3 study treatments, the EOT visit should be performed within 1 week but the subject should be followed up according to the schedule of assessments until end of study (EOS; as defined below).

[7] EOS is defined as the last data collection for a subject. The EOS visit for all subjects (regardless of whether they are receiving 3, 2, 1, or no study treatment) is planned approximately 5 months after the EOMOP visit. For all randomized patients, follow-up for disease progression (including death) will continue until EOS.

EOMOP = end of main observation period; EOS = end of study; EOT = end-of-treatment; RHC = right heart catheterization.

Figure 2 Planned duration (study level)



*See Figure 1 for abbreviations and definitions

The database will be partially locked once all subjects have performed their end of main observation period (EOMOP) visit (or prematurely discontinued from the study). Unblinding will follow the partial database lock. Unless otherwise specified, the analyses described in this SAP will be performed on this set of data including all data up to EOMOP. Once all subjects have undergone their end-of-treatment (EOT) and end-of-study (EOS) visits the database will be fully locked. Some analyses [see Section 13] will be performed including all data up to EOS.

2.2 Study visit and assessment schedule

Please refer to the protocol [D-18.392] for schedule of visits and assessments.

3 OBJECTIVES

3.1 Primary objective(s)

The primary objective of the study is to compare the effect on PVR of an initial triple oral regimen (macitentan, tadalafil, selexipag) versus an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH.

3.2 Secondary objective(s)

The secondary objective of the study is to compare an initial triple oral regimen (macitentan, tadalafil, selexipag) with an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH, with respect to exercise capacity, cardio pulmonary hemodynamics (other than PVR), disease severity, disease progression events, safety, and tolerability.

3.3 Other objective(s)

The exploratory objective of the study is to compare an initial triple oral regimen (macitentan, tadalafil, selexipag) with an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH, with respect to additional disease severity endpoints.

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

The order of hierarchical testing for secondary endpoints is modified as compared to the protocol. The change from Baseline to Week 26 in six-minute walk distance (6MWD) is promoted as the first secondary endpoint in the hierarchical testing strategy.

As a result, statistical analyses for secondary endpoints will be performed in the following sequence:

1. Change from baseline to Week 26 in 6MWD
2. Change from baseline to Week 26 in N-terminal pro B-type natriuretic peptide (NT-proBNP).
3. Time from randomization to first disease progression event up to EOMOP + 7 days
4. Absence of worsening from baseline to Week 26 in WHO FC

This change is performed following interaction with the Food and Drug Administration (FDA; teleconference [TC] on 2 November 2017). The protocol is not amended for this purpose due to insufficient time to implement this change prior to the pre-planned interim analysis for futility. This will be added at a later stage in a protocol amendment (if any).

4.2 Changes in the conduct of the study / data collection

Following a protocol amendment to increase sample size (protocol version 4 [D-18.392]), new countries are participating in the study. The level of randomization stratification factor "Europe" is re-labeled as "Rest of World" to include those new countries and ensure that it does not affect the original randomization list.

4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

Clarifications have been added for PVR calculation when pulmonary capillary wedge pressure (PCWP) / left ventricular end diastolic pressure (LVEDP) at a given visit is missing, as described in Section 10.6.2.2. Sensitivity analyses have been added for primary and secondary efficacy analyses.

In addition, primary efficacy endpoint and first secondary efficacy endpoint have been described in terms of estimands [Table 2 and Table 3, respectively].

5 DEFINITIONS OF VARIABLES

5.1 Screened failures

Screened subjects are subjects who received a subject number. Screened failures are subjects who receive a subject number but are not randomized. If a patient is not randomized, the reason is collected in the eCRF.

5.2 Subject characteristics

Unless stated otherwise, if a subject is re-screened and baseline, demographics, or other characteristics are collected again, the latest assessments from the re-screening are used for analysis.

5.2.1 Demographics

Demographics are collected at screening and comprise age, sex, race, ethnicity, region, height, weight, body mass index (BMI) and body surface area (BSA).

Although BSA and BMI are computed by the eCRF, the statistical analysis only considers the re-calculated values using weight and height.

5.2.2 Baseline disease characteristics

Etiology of PAH, association of PAH with other diseases, as well as WHO FC are collected at screening. The time since the initial diagnosis of PAH to the randomization date is summarized in days.

A right heart catheterization (RHC) is performed and hemodynamic parameters – PVR (dyne.sec.cm^{-5}), mean pulmonary arterial pressure (mPAP; mmHg), systolic/diastolic pulmonary arterial pressure (mmHg), systolic/diastolic systemic arterial pressure (mmHg),

PCWP (mmHg), LVEDP (mmHg), mean right atrial pressure (mRAP; mmHg), cardiac output (CO; L/min), total pulmonary resistance (TPR; dyne.sec.cm^{-5}), cardiac index (CI; L/min/m^2) – are determined.

PVR, TPR and CI that are derived by the eCRF are listed only. The results from the sponsor-re-calculated PVR in the analysis database are used for analysis [see Section 5.5.1 for formula used]. In addition, PVR is also reported by the investigator and is listed along with the other hemodynamic parameters, and also summarized together with the sponsor-re-calculated PVR in the baseline characteristics tables.

If investigator-reported PVR is entered as Wood units, it is converted to dyne.sec.cm^{-5} for analysis. The conversion follows the rule:

80 dyne.sec.cm^{-5} = 1 mmHg.min.L^{-1} (Wood units)

5.2.3 Other baseline characteristics

A six-minute-walk test is performed at screening and on the day of randomization. The occurrence and reasons for stopping the test prematurely are collected, as well as the need for supplemental oxygen. After the test, the Borg dyspnea score is assessed in each subject.

Baseline vital signs (pulse and systolic/diastolic blood pressure) are assessed at screening and on the day of randomization.

A physical examination is conducted at screening. Existing abnormalities are identified and their clinical significance is determined.

5.2.4 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 was ongoing at screening visit or not. The diagnosis is coded using the most current version of the MedDRA dictionary at the time of the database closure.

5.2.5 Previous and concomitant therapies

Previous and concomitant therapies are collected at every visit in the CRF. Missing or incomplete medication start and end dates are imputed as described in Section 12.1 in order to assign the dates to one of the categories below.

5.2.5.1 Previous therapies

A previous therapy is any treatment for which the end date of treatment is prior to Day 1.

5.2.5.2 Baseline-concomitant therapies

A baseline-concomitant therapy is any treatment that is ongoing at start of macitentan and tadalafil (as per CRF tick box) or that started prior to study treatment and is ongoing at Day 1, i.e., not stopped prior to Day 1.

5.2.5.3 Study-treatment-concomitant therapies

A study-treatment-concomitant therapy is any treatment that is administered at any time between the start of the first study treatment (Day 1) and discontinuation of the last study treatment (EOT).

5.3 Study treatment exposure

In this study, three different study drugs are investigated: macitentan, tadalafil, and selexipag/placebo. With the exception of macitentan, doses are not fixed and can be titrated.

5.3.1 Exposure to study drugs

5.3.1.1 Exposure to macitentan (days)

Macitentan is given once daily in oral form in a fixed dose. Exposure to macitentan is computed as the number of days between first and last dose of macitentan, regardless of any treatment interruptions.

5.3.1.2 Exposure to tadalafil (days)

Tadalafil treatment is started as a single 20 mg oral dose and subjects are up-titrated to a 40 mg single dose after one week. Exposure to tadalafil, regardless of dose, is defined as the number of days between the first dose (i.e., first intake) and the last dose of tadalafil, regardless of treatment interruptions or titrations.

5.3.1.3 Exposure to selexipag/placebo (days)

Selexipag/placebo is administered in a double-blind manner, through two dosing periods.

- A titration period, which starts 15 days after randomization as a twice daily (b.i.d.) oral dose of 200 µg and is up-titrated on a weekly basis thereafter until the 1600 µg b.i.d. maximum dose or the maximum tolerated dose (MTD) is reached. The titration period ends on the day of the Week 12 visit of the subject.

- A maintenance period, which follows the titration period, during which the dose of selexipag/placebo is maintained constant except dose adjustment for safety. The maintenance period starts on the day after the Week 12 visit of the subject.

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 (i.e., first intake) and the last dose of selexipag/placebo medication, regardless of interruptions or titrations.

5.3.1.3.1 Selexipag/placebo maximum tolerated dose

The MTD is defined as the selexipag/placebo dose (b.i.d) taken by the subject on the day after the Week 12 visit. It is 0 for patients with study drug discontinuation prior to or at the Week 12 visit, whatever the reason is.

5.3.1.3.2 Selexipag/placebo individual maintenance dose

For patients who enter the maintenance period, the individual maintenance dose (IMD) is defined as the daily selexipag/placebo dose (b.i.d) to which the subject is exposed to for the longest time (i.e., maximum number of days) during the maintenance period, i.e., after the day of the Week 12 visit. If more than one selexipag/placebo dose corresponds to the maximum number of days during the maintenance period, the highest dose (b.i.d) is considered.

For patients with a last selexipag/placebo dose intake prior to the maintenance period, the IMD is the maximum selexipag/placebo dose (b.i.d) that did not lead to study drug discontinuation or down-titration of selexipag/placebo.

For patients who received only the lowest selexipag/placebo dose level of 200 µg b.i.d., the IMD is 200 µg if selexipag/placebo was not discontinued prematurely (as recorded on specific eCRF "Premature Discontinuation of Study Treatment - Selexipag/Placebo" page), otherwise it is set to 0 µg.

For each subject, the following selexipag/placebo doses are analyzed:

- Maximum and weighted-average selexipag/placebo dose in the titration period
- Maximum and weighted-average selexipag/placebo dose in the maintenance period (for patients who entered this period)
- Maximum and weighted-average selexipag/placebo dose in the entire treatment period
- Selexipag/placebo MTD [see Section 5.3.1.3.1]
- Selexipag/placebo IMD [see Section 5.3.1.3.2]

The b.i.d dose (between 200 µg and 1600 µg) is used for analysis.

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

5.3.1.3.3 Selexipag/placebo individual maximum tolerated dose

For patients who completed the titration period, individual maximum tolerated dose (IMTD) is defined as the last selexipag/placebo dose (b.i.d) taken at the end of titration period (i.e., at the day of the Week 12 visit). For patients who did not enter to the maintenance period, IMTD is defined as the latest selexipag/placebo dose (b.i.d) that did not lead to study drug discontinuation or down-titration of selexipag/placebo.

- If the latest daily dose (b.i.d) is 200 mcg with the above reasons, IMTD is defined as zero.

5.3.1.4 Exposure to combinations (days)

Overall exposure to combinations "at least macitentan + tadalafil" and "at least macitentan + tadalafil + selexipag/placebo" regardless of dose is defined as the number of days between the first dose (i.e., first intake) of concomitant combination and the last dose of concomitant medication, regardless of interruptions or titrations.

5.3.2 Study treatment discontinuation

Each of the three study medications can be discontinued permanently (as recorded on the specific eCRF page "Premature Discontinuation of Study Treatment" for each treatment) while the remaining treatment(s) are continued.

The reasons for premature discontinuation of each treatment are collected in the eCRF on separate pages. In case the patient has prematurely discontinued study (e.g., if the patient died) and did not provide reasons for premature discontinuation of individual study treatments, the information from the study discontinuation page is used to determine the reason for premature treatment discontinuation.

5.3.3 Study treatment adjustments or interruptions

The reasons for study drug adjustments or interruptions are collected on a separate eCRF page for each dose level or dose end of the three study treatments, together with the start and end date of the treatment and the dose.

5.4 Study discontinuation

Study discontinuation includes all subjects, i.e., those who prematurely discontinued and those who completed the study as per protocol.

For subjects who prematurely discontinued the study, the associated reason(s) are entered in the eCRF.

5.5 Efficacy variables

5.5.1 Primary efficacy variable

The primary efficacy variable is the ratio of Week 26 to baseline PVR (Week 26 divided by baseline). PVR is determined by RHC at screening and Week 26. Although PVR is collected in the eCRF as reported by the investigator (and eCRF-derived), the sponsor-re-calculated PVR is used for the analysis, applying the following formula:

$$PVR\ (dyne.sec.cm^{-5}) = (\ (\ mPAP - PCWP\ [or\ LVEDP\ if\ PCWP\ is\ missing]\ )\ /\ CO) * 80$$

PCWP and LVEDP are recorded as two separated fields for this study, and therefore LVEDP can be used in case PCWP is missing [see Appendix 1].

5.5.2 Secondary efficacy variables

5.5.2.1 Change from baseline to Week 26 in six-minute walk distance

The change from baseline to Week 26 in 6MWD is calculated as Week 26 minus baseline. 6MWD is determined at the screening visit, randomization visit (if more than seven days after screening visit), at Week 12, at Week 26, and then every six months as well as at EOMOP and EOT visits. The distance is entered in meters in the eCRF.

5.5.2.2 Change from baseline to Week 26 in NT-proBNP

The change from baseline to Week 26 in NT-proBNP is expressed as the ratio of Week 26 to baseline NT-proBNP (Week 26 divided by baseline). NT-proBNP is determined at the screening visit, randomization visit (if more than seven days after screening visit), Week 12, Week 26, and then every six months as well as at EOMOP and EOT visits. It is determined by the central or local laboratory [see also Section 5.6.9]. NT-proBNP values are expressed in unit ng/L for analysis.

5.5.2.3 Absence of worsening from baseline to Week 26 in WHO FC

WHO FC is determined at the screening visit, randomization visit (if more than seven days after screening visit), at Week 12, at Week 26, and then every six months as well as at EOMOP and EOT visits. The WHO FC assessment (I to IV) is directly entered in the eCRF.

5.5.2.3.1 Absence of worsening from baseline to Week 26, Version I

Worsening of WHO FC at Week 26 is determined in patients who are in WHO FC I, II, or III at baseline. Worsening of WHO FC occurs when a worse WHO FC (higher) than baseline is observed at the Week 26 visit. After the final WHO FC assessment, worsening of PAH status cannot be determined. Worsening of WHO FC cannot be determined in patients who already have Class IV at baseline.

5.5.2.3.2 Absence of worsening from baseline to Week 26, Version II

An alternate version of the endpoint is generated for patients in WHO FC IV: a worsening occurs if the patient has died or has been hospitalized due to PAH (as adjudicated by the Clinical Events Committee [CEC]) before Week 26. If the WHO FC has improved at Week 26, the patient has absence of worsening, regardless of PAH-related hospitalizations.

To ensure comparability with the endpoint definition in Version 1, the date of worsening is assigned to a scheduled visit date where WHO FC was assessed: the assignment of assessments to visits is done using the time windowing for WHO FC [see Section 11.4]. After the last visit where a WHO FC assessment is planned (usually the EOT visit), the endpoint is not determined.

5.5.2.4 Change from baseline to Week 26 in hemodynamic variables other than PVR

The change from baseline to Week 26 in hemodynamic variables other than PVR is calculated as Week 26 minus baseline. Variables are:

- mPAP
- CI, which is re-derived as the ratio of CO and re-calculated BSA
- TPR, which is re-derived as *80 × (mPAP/CO)*
- mRAP
- Venous oxygen saturation

BSA, TPR and CI are derived by the eCRF and re-calculated by analysis programming. Both values are listed; the re-calculated values are used for analysis.

5.5.2.5 Time to the first disease progression event up to EOMOP + 7 days

Time from randomization to the first disease progression event up to EOMOP + 7 days as adjudicated by the CEC, defined as any of the following:

a. Death

b. Hospitalization for worsening PAH.

c. Initiation of prostacyclin, a prostacyclin analog, or a prostacyclin receptor agonist for worsening PAH.

d. Clinical worsening defined as a post-baseline decrease in 6MWD by > 15% from the highest 6MWD obtained at or after screening, accompanied (same day) by WHO FC III or IV (both conditions confirmed at two consecutive post-baseline visits separated by 1–21 days).

All events are adjudicated by the CEC. The start date of the event provided by the CEC is used for time-to-event analyses.

If two events were observed on the same day, e.g., hospitalization due to worsening of PAH and initiation of prostacyclin on the same day, the most severe one is considered as the first event. The severity is given in descending order from a) to d) above. All events will be listed.

5.5.3 Other efficacy variables

5.5.3.1 Changes of secondary efficacy endpoints from baseline to EOMOP

6MWD, NT-proBNP and WHO FC are collected regularly as described in Section 5.5.2. Changes from baseline to the scheduled collection time points up to EOMOP are computed.

Additional hemodynamic parameters collected in the RHC are listed.

5.5.3.2 Unsatisfactory clinical response

Unsatisfactory clinical response is computed for Week 26 and all regular visits after Week 26, i.e., Month 12, Month 18, Month 24, etc. until EOMOP.

It is defined as the occurrence of at least one of the following criteria:

- WHO FC III or IV at the time of the visit
- Both 6MWD ≤ 440 m and NT-proBNP ≥ 3 × upper limit of normal (ULN; must be at the same visit) at the time of the visit.
- Clinical worsening as defined in Section 5.5.2.5, part d up to and including the analysis visit but ignoring all assessments prior to Week 26.

If one or more of the criteria are not assessed at a study visit, the last value of the respective assessment is carried forward (including baseline value) unless a disease progression event [see Section 5.5.2.5] has occurred after the last non-missing assessment.

5.5.3.3 Number of treatment goals met at Week 26

The number of treatment goals met is derived at Week 26. The number of treatment goals achieved is added up and thus achieve a score of 0 to 5 points. Three different versions of treatment goals are determined.

5.5.3.3.1 Treatment goals Version 1 (McLaughlin I)

- WHO FC I or II
- CI > 3 L/min/m^2
- mRAP < 8 mmHg
- 6MWD > 440 m
- NT-proBNP < 3 × ULN

5.5.3.3.2 Treatment goals Version 2 (McLaughlin II)

The cut-off value for CI is changed compared to Version 1:

- WHO FC I or II
- CI > 2.5 L/min/m^2
- mRAP < 8 mmHg
- 6MWD > 440 m
- NT-proBNP < 3 × ULN

5.5.3.3.3 Treatment goals Version 3 (Nickel)

The cut-off value for NT-proBNP is changed compared to Version 1:

- WHO FC I or II
- CI > 3 L/min/m^2
- mRAP < 8 mmHg
- 6MWD > 440 m
- NT-proBNP < 1800 ng/L

5.5.3.3.4 Treatment goals Version 4 (Galiè)

The cut-off value for CI and NT-proBNP are changed compared to Version 1:

- WHO FC I or II
- CI ≥ 2.5 L/min/m^2
- mRAP < 8 mmHg
- 6MWD > 440 m
- NT-proBNP < 300 ng/L

If one or more assessment(s) for a treatment goal at Week 26 is missing, the last value of the respective assessment is carried forward (including baseline value) unless a disease progression event [see Section 5.5.2.5] has occurred after the last non-missing assessment. In this case, the treatment goal(s) carried forward are counted as not reached. Missing treatment goals after imputation are considered as not met.

5.5.3.4 Improvement of WHO FC from baseline to Week 26

Improvement of WHO FC at Week 26 is determined in patients who are in WHO FC II, III or IV at baseline. Improvement of WHO FC occurs when the WHO FC at Week 26 visit is lower than the one observed at baseline. Improvement of WHO FC cannot be determined in patients who already have Class I at baseline.

5.5.3.5 Hospitalizations up to EOMOP

The following endpoints related to hospitalizations are defined. All-causes hospitalizations refer to any hospitalization as documented in the AE eCRF pages. Hospitalizations for worsening PAH are those as adjudicated by the CEC.

In case of missing or incomplete hospital admission / discharge date, imputations of missing date parts are made as described in Section 12.4.

5.5.3.5.1 Time from randomization to first hospitalization (all causes) up to EOMOP

The date of first hospitalization is the date of the first admission date as collected in the AE eCRF pages (from randomization up to EOMOP visit date). Subjects with no hospitalizations will be censored at min (EOS, EOMOP) date.

5.5.3.5.2 Time from randomization to first hospitalization for worsening PAH up to EOMOP

The date of first hospitalization for worsening PAH is the date of the first worsening PAH event date as adjudicated by CEC (Adjudicator 1) from randomization up to EOMOP visit date.

Subjects with no hospitalizations will be censored at min (EOS, EOMOP) date.

5.5.3.5.3 Annualized rate of hospitalization (all causes) up to EOMOP

The number of hospitalizations (all causes) initiated from randomization up to min (EOS, EOMOP) visit is annualized by multiplying with 365.25 divided by (min [EOS, EOMOP] date - randomization date +1).

5.5.3.5.4 Annualized rate of hospitalization for worsening PAH up to EOMOP

The number of hospitalizations for worsening PAH initiated from randomization up to min (EOS, EOMOP) visit is annualized by multiplying with 365.25 divided by ((min [EOS, EOMOP] date - randomization date +1).

5.5.3.5.5 Annualized rate of days spent in hospital (all causes) up to EOMOP

For each hospitalization (all causes), the number of days spent in hospital up to EOMOP is calculated as min (EOS, EOMOP, discharge date) - admission date + 1. For each subject, the number of days spent in hospital up to EOMOP is the sum of the number of days spent in hospital up to EOMOP. In case the admission date of a new hospitalization occurs prior to or on the discharge date of a previous hospitalization, the day is counted only once.

The number of days spent in hospital (all causes) is annualized by multiplying with 365.25 divided by ((min [EOS, EOMOP] date - randomization date +1).

In case of missing discharge date: if admission date is not missing or if 'hospitalization required' is ticked 'yes', the min (EOS, EOMOP) visit date is used for the analysis up to EOMOP.

5.5.3.5.6 Annualized rate of days spent in hospital for worsening PAH up to EOMOP

The annualized rate of days spent in hospital for worsening PAH up to EOMOP is defined as in Section 5.5.3.5.5 but restricted only to hospitalization for worsening PAH.

5.6 Safety variables

5.6.1 Adverse events

Adverse events (AEs) are collected in the eCRF. In case of missing or incomplete AE start and/or stop dates, imputations of missing date parts are made as described in Section 12.2 to determine date of onset and resolution for analysis.

5.6.1.1 Treatment-emergent adverse events

Treatment-emergent AEs are defined as those AEs occurring from the day of treatment start of the first of the three study medications (Day 1) up to 30 days after study treatment end date of the last of the three study medications.

5.6.1.2 Frequency of treatment-emergent adverse events

Treatment-emergent AEs reported more than once within a subject at the Preferred Term (PT) level 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 subject, the worst intensity is considered. AEs with missing intensity are considered in any analysis with the worst intensity.

5.6.1.4 Relationship of treatment-emergent adverse events

Relationship to study treatment is defined as 'related' or 'not related'. For treatment-emergent AEs reported more than once within a subject, the worst relationship is considered; i.e., AEs reported both as related and unrelated are counted as related.

AEs with missing relationship are considered in any analysis as related.

5.6.2 Deaths

All AEs with outcome 'death' are reported. The reason for death is captured on a separate eCRF page.

5.6.3 Serious adverse events

Serious adverse events (SAEs) are events that are marked as serious in the eCRF. AEs with missing seriousness are considered as serious.

5.6.4 Non-serious adverse events

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.

5.6.5 Adverse events leading to discontinuation of study treatment

AEs with Action 'Permanently discontinued' for any of the three study medications are considered AEs leading to discontinuation of study treatment.

5.6.6 Other significant adverse events

Important identified or potential risks for selexipag are given below. The definitions are based on a combination of preferred terms, high level terms, low level terms, system organ class (SOC) and SMQs (Standardized MedDRA Queries) which can be updated according to MedDRA/SMQs updates or finding of new safety signal(s). Details of the categories below will be provided in "AESI definition file" that will be saved and version controlled in the Entimo Integrated Clinical Environment (or equivalent system).

- Hypotension
- Anemia
- Hyperthyroidism
- Major adverse cardiovascular event
- Acute renal failure and renal function impairment
- Bleeding events

- Light-dependent non-melanoma skin malignancies
- Ophthalmological effects associated with retinal vascular system
- Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
- Medication errors.
- Off-label use
- Pregnancy
- Pulmonary venoocclusive disease associated with pulmonary oedema

In addition, symptomatic hypotension AEs are investigated.

AEs typical of prostanoid treatments are also investigated. They will be retrieved 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.

5.6.7 Vital signs and body weight

Vital signs (weight [kg], BMI [kg/m^2], pulse rate [bpm], systolic/diastolic blood pressure [mmHg] and the location of measurement) are collected.

5.6.8 Electrocardiogram

Electrocardiography (ECG) is not assessed in this trial.

5.6.9 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 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.

Local laboratory values will only be used if no corresponding central laboratory value is available.

The following parameters are evaluated:

5.6.9.1 Hematology tests

- Hemoglobin
- Hematocrit
- Erythrocyte count (reticulocyte count)
- Leukocyte count with differential counts
- Platelet count

5.6.9.2 Biochemistry tests

- Aminotransferases (aspartate aminotransferase [AST] / alanine aminotransferase [ALT]), alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase
- Creatinine, urea
- Creatinine clearance (Cockcroft-Gault formula)
- Uric acid (serum urate)
- Glucose
- Sodium, potassium, chloride, calcium
- Protein, albumin

5.6.9.3 Coagulation tests

- International Normalized Ratio
- Prothrombin time
- Activated partial thromboplastin time

5.6.9.4 Pregnancy tests

Urine pregnancy tests at the Day 1 visit and monthly outside of scheduled visits after Week 26.

5.6.9.5 Biomarkers

NT-proBNP is analyzed as an efficacy endpoint.

The analysis of circulating biomarkers involved in right ventricular function and structure is described in a separate document. The list of biomarkers to be measured after the end of the study will be based on the latest scientific evidence regarding right ventricular function and structure at the time of laboratory analysis [D-18.392, section 6.3].

5.6.9.6 Schedule of assessments

Liver function tests (AST/ALT) and hemoglobin values are evaluated in monthly intervals up to Week 26, while the general laboratory tests take place at Week 12, Week 26, and every visit thereafter.

Serum pregnancy tests occur at all scheduled visits except the Day 1 visit, and monthly until Week 26. Urine pregnancy tests occur at the Day 1 visit and monthly outside of scheduled visits after Week 26.

In Sweden, serum pregnancy tests occur at all scheduled visits except the Day 1 visit, and monthly until the EOT visit. Urine pregnancy tests occur at the Day 1 visit and EOS visit.

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 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 includes all subjects who were screened and received a subject number.

7.1.2 Full analysis set

The full analysis set (FAS) includes all randomized subjects. Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received).

7.1.3 Modified Full Analysis Set

The modified full analysis Set (mFAS) includes all subjects from the FAS who received at least one dose of each of the three study treatments (macitentan, tadalafil, and double-blind selexipag or placebo). Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received).

7.1.4 Per-protocol analysis set

The per-protocol analysis set (PPS) includes all subjects from the FAS who received at least one dose of double-blind study treatment and who have no major protocol deviation.

The PPS are defined in a blinded fashion prior to unblinding of the study.

The major deviations leading to exclusion of PPS are:

- Deviation at Screening/Re-screening and Randomization: PD102, PD106, PD107, PD108, PD111, PD112, PD113, PD114, PD120, PD121, PD131,
- PD after Randomization: PD214, PD215, PD216, PD220, PD221, PD222, PD210, PD226 (only if occurred prior to Week 26).

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

7.1.5 Safety analysis set

The Safety analysis set (SAF) includes all subjects who received at least one dose of any of the three study treatments. The patients are analyzed as actually treated. If the actual treatment arm cannot be determined (e.g., if no double-blinded study medication has been received or both placebo and selexipag have been received), patients are assigned to the selexipag arm if they received at least one dose of selexipag, otherwise to the placebo arm. For subjects included in the SAF, the actual treatment is equal to the randomized treatment except for subjects randomized to placebo who received at least one dose of selexipag (if a wrong kit was received as documented in the comment field of PD226 and if this kit was received prior to EOMOP and corresponds to selexipag treatment).

Safety analyses specific to one study medication (e.g., treatment emergent adverse events related to macitentan) will be restricted to the subset of subjects from the SAF who received at least one dose of the corresponding study medication.

7.2 Usage of the analysis sets

The usage of the analysis sets is summarized in Table 1.

Table 1 Overview of the different analysis sets and their usage

Analyses/Data Displays	Screened analysis set	Full analysis set	Modified full analysis set[2]	Safety analysis set	Per protocol set
Patient disposition	✓				
Inclusion /exclusion criteria	✓				
Demographics		✓	✓		✓
Baseline characteristics		✓	✓		✓
Medical history		✓	✓		
Previous and concomitant medications		✓	✓		
Treatment exposure				✓	✓
Efficacy: Primary endpoint		✓	✓[1]		✓
Efficacy: Secondary endpoints		✓	✓[1]		✓
Efficacy: Exploratory endpoints		✓			
Safety endpoints				✓	
All subject listings	✓				

[1] A sensitivity analysis is run on all patients who took all three study medications up to the Week 26 visit.
[2] Analyses on the modified full analysis set are shown if the full analysis set and modified full analysis set are different by at least 5% in the total number of patients.

8 DEFINITION OF SUBGROUPS

Subgroup analyses are planned on the stratification factors: region (North America versus rest of the world) and WHO FC (FC I/II vs FC III/IV). Additional subgroup analyses will be conducted for gender (male vs female), age (64 or lower vs ≥ 65 years) and PAH etiology (idiopathic PAH, heritable PAH, drug- or toxin-induced PAH, PAH associated with connective tissue disease [CTD], PAH associated with Others).

9 GENERAL STATISTICAL METHODOLOGY

All statistical analyses are run by the contract research organization Datamap GmbH, Freiburg, Germany (under Actelion supervision), using statistical analysis system (SAS) 9.3 or higher on a SUN Solaris system.

9.1 Design of the study

The study uses a group sequential design with an interim analysis (IA) for futility, which will be conducted when 33% of the patients have completed the primary efficacy endpoint assessment (Week 26 PVR assessment) or prematurely discontinued. The IA will be conducted by an ISAC for the IDMC who will provide Actelion with their recommendation to either continue or prematurely terminate the study for futility [see also Section 10.1 and IDMC charter].

The main efficacy analysis will be conducted when all patients have completed the primary efficacy endpoint assessment.

Safety and secondary efficacy data are collected afterwards until the patients reach the EOT visit (4 months after EOMOP visit). Further safety data is collected until EOS (5 months after EOMOP visit). All data collected after Week 26 visit up to EOMOP visit will be analyzed using descriptive methods but not be used for inferential statistics.

This SAP also describes the blinded outputs provided on a regular basis for IDMC open session meetings (see IDMC charter). Those blinded outputs for IDMC are a subset of CSR outputs and are flagged accordingly in a list of outputs provided in Section 13.

The unblinded analyses for IDMC closed sessions (including futility interim analysis) are performed by the ISAC according to ISAC's own analysis plan. The study team remains blinded. The ISAC is responsible for the content of these unblinded analyses for the closed reports provided to the IDMC (see IDMC charter).

9.2 Statistical methods used for the primary endpoint

The primary endpoint will be analyzed on the FAS. The primary efficacy endpoint is the ratio of Week 26 to baseline PVR using re-calculated PVR and a last observation carried forward (LOCF) approach, i.e., the last observation including baseline is carried forward towards Week 26.

To obtain the ratio of Week 26 to baseline, PVR is log-transformed (base e). The change of log-transformed PVR values is analyzed using an analysis of covariance (ANCOVA) model with treatment arm and stratification factors region and WHO FC as factors and baseline log-transformed PVR as covariate. The estimated least squares mean is computed for the treatment group difference (triple therapy - dual therapy) on a log scale. The point estimates for treatment group difference and 95% confidence intervals are exponentiated and displayed, thus representing the ratio of geometric means of the relative treatment effect on PVR.

Superiority of the triple combination is achieved if the complete confidence interval for the geometric means ratio is below 1. This is equivalent to the upper limit of the confidence interval for treatment mean difference of values on a log scale being smaller than zero.

Distributional assumptions are assessed graphically. Single-slope assumptions in both treatment groups are assessed by investigating treatment-by-covariate interaction added to the ANCOVA model.

The following SAS code is used for analysis:

```
PROC MIXED DATA=dataset;
CLASS treatment stratum1 stratum2;
MODEL logpvrratio=treatment stratum1 stratum2 baselogpvr;
LSMEANS treatment /PDIFF CL ALPHA=0.05;
RUN;
```

9.3 Analysis of covariance for secondary efficacy parameters

ANCOVA models for change from baseline to Week 26 are similar to the model used for the primary endpoint. They include the randomization strata (region and WHO FC) and treatment groups as factors as well as the baseline value as covariate. The 95% confidence intervals are computed for treatment group difference.

Distributional assumptions are assessed graphically. Single-slope assumptions in both treatment groups are assessed by investigating treatment-by-covariate interaction added to the ANCOVA model.

SAS code, similar to the following is used for analysis:

```
PROC MIXED DATA=dataset;
WHERE visitvariable = 'Week 26 Visit';
CLASS treatment stratum1 stratum2;
MODEL value=treatment stratum1 stratum2 baseline;
LSMEANS treatment /PDIFF CL ALPHA=0.05;
RUN;
```

6MWD, and hemodynamic variables from RHC are analyzed in this fashion (main analysis for those endpoints).

The main analysis for NT-proBNP is the same as for PVR, as described in Section 9.2.

9.4 Logistic regression for dichotomous outcomes

Logistic regression models for dichotomous outcomes include the treatment group, the baseline stratification variables (region and WHO FC) unless stated otherwise. The odds ratio with 95% Wald confidence intervals are computed for treatment group difference.

SAS code, similar to the following is used for analysis:

```
PROC LOGISTIC DATA=dataset;
WHERE visitvariable = 'Week 26 Visit';
CLASS treatment stratum1 stratum2 ;
MODEL value (event='Yes') =treatment stratum1 stratum2 /CLODDS=WALD
ALPHA=0.05;
RUN;
```

Absence of worsening from baseline to Week 26 is analyzed in this fashion. In case of too few events, an exact logistic regression may be used.

9.5 Time to event analyses

All event and censoring times are on a day/date scale.

Kaplan-Meier (KM) type analyses are planned for analyses of time-to event endpoints to obtain product-limit survival estimates as well as median survival times. To assess treatment effect, stratified log-rank test for treatment group difference stratified for the randomization strata is computed. Furthermore, a Cox (proportional hazard) regression model with randomization strata and treatment arm as factors is computed. The hazard ratio for treatment arms is computed together with the corresponding 95% confidence interval.

Furthermore, 95% confidence intervals are computed for the KM estimators using Greenwood's formula. Proportional hazard assumption is assessed graphically.

SAS code, similar to the following, is used for analysis:

```
* Obtain KM estimates *;
PROC LIFETEST DATA=dataset METHOD=km STDERR;
BY treatment;
TIME day*censor(1);
RUN;

* Log Rank Test *;
PROC LIFETEST DATA=dataset METHOD=km;
TIME day*censor(1);
STRATA stratum1 stratum2/GROUP=treatment TEST=logrank;
RUN;

* Cox Regression *;
PROC PHREG DATA=dataset;
CLASS treatment (ref="Placebo");
MODEL day*censor(1)=treatment /RL;
STRATA stratum1 stratum2;
RUN;
```

Time to the first disease progression event and time to first hospitalization (without stratum 1 and stratum 2) is analyzed in this fashion.

9.6 Mixed model repeated measures analyses

For mixed model repeated measures analyses (MMRM) up to Week 26 (sensitivity analyses for 6MWD and NT-proBNP), the dependent variable is analyzed using treatment arm, randomization strata, visit and visit by treatment interaction term as factors. The baseline value of the dependent variable is used as a continuous covariate. Repeated measures of the response variable within the same subject are considered correlated with an unstructured covariance matrix. Fixed-effect tests are computed using the Kenward-Rogers method to determine the degrees of freedom for the denominator. Treatment group differences are computed using appropriate contrasts for the treatment and treatment by visit interaction terms. The 95% confidence intervals are computed together with the treatment contrasts. Distributional assumptions are assessed graphically.

SAS code, similar to the following, is used for analysis. Note that the treatment contrasts depend on the number of visits included in the model and thus may be replaced by an equivalent SLICE statement to allow for a variable number of visits included in the model.

```
PROC MIXED DATA=dataset;
CLASS treatment visit stratum1 stratum2 subj_id;
MODEL value = treatment visit stratum1 stratum2 treatment*visit baseline /DDFM=KR;
REPEATED visit / SUBJECT=subj_id /TYPE=UN;
ESTIMATE 'Selexipag - Placebo, overall'
 treatment 1 -1 /C L ALPHA=0.05;
ESTIMATE 'Selexipag - Placebo, Month 1'
 treatment 1 -1
 treatment*visit 1 0 0 0 0 -1 0 0 0 0 /CL ALPHA=0.05;
ESTIMATE 'Selexipag - Placebo, Month 2'
 treatment 1 -1
 treatment*visit 0 1 0 0 0 0 -1 0 0 0 /CL ALPHA=0.05;
…
RUN;
```

Change of 6MWD from baseline to all regular collection time points (up to Week 26) are analyzed in this fashion.

Change of NT-proBNP is analyzed on a log scale and the results will be exponentiated to obtain geometric means and geometric mean ratios at each visit (up to Week 26).

9.7 Cochran-Mantel-Haenszel test for categorical outcomes

The Cochran-Mantel-Haenszel (CMH) test assesses treatment arm differences adjusting for stratification variables in categorical outcomes. Outcomes with more than one category, e.g., number of treatment goals met, must be on an ordinal scale. Mean CMH scores are computed for each treatment arm and the results are tested.

SAS code, similar to the following, is used for analysis. Note that the order of variables in the TABLES statement is critical to compute the proper CMH statistic. The CMH test statistic for 'Row mean scores differ' is used for analysis.

```
PROC FREQ DATA=dataset;
TABLES stratum1*stratum2*treatment*outcome /CMH;
RUN;
```

The number of treatment goals met is analyzed in this fashion.

9.8 Multiple imputation method analysis

Multiple imputation (MI) analysis (under missing at random assumption) replaces each missing endpoint by a set of 50 plausible values, each set with a different value for the SAS variable _imputation_.

A linear regression model is fitted using observations with observed values by treatment group for the endpoint and baseline covariates. Based on the fitted regression model, a new regression model is simulated from the Bayesian posterior predictive distribution of the regression parameters and is used to impute the missing values. For each missing value, a predicted value is computed from the regression model. Then, a set of five observations, whose corresponding predicted values are closest to the predicted values, is generated. The missing value is then replaced by a value drawn randomly from these five observations. Each imputation is then analyzed using the statistical model for the complete endpoint; the estimates are back transformed to normal scale (if applicable) and the results from the 50 imputations are aggregated using Rubin's rule.

```
PROC MI DATA=dataset OUT=mi_dataset nimpute=50 seed=<random 515448>;
BY treatment; * Selexipag should be first ** ;
VAR base endpoint;
MONOTONE REGPREDMEANMATCH (endpoint=base)
RUN;

PROC MIXED data=mi_dataset …. /* as for the primary endpoint */;
by _imputation_;
CLASS …/* statements as for the primary endpoint */;
RUN;

PROC MIANALYZE PARMS=mixed_out;
CLASS treatment;
MODELEFFECTS treatment difference;
RUN;
```

9.9 Analysis method for counts and rates

For the annualized rate of events (e.g., hospitalization) up to EOMOP, a generalized linear model with Poisson distribution and log of time at risk as an offset is assumed.

For each treatment group, the 95% confidence limit of the annualized event rate will be computed and in addition the 95% confidence limits of the relative reduction in mean annualized event rate for selexipag compared to placebo will be computed using SAS PROC GENMOD as below.

PROC GENMOD DATA=dataset;

CLASS treatment (ref='Placebo') ;

MODEL Nevent = treatment / dist=poisson link=log offset=ltime;

ESTIMATE "Selexipag rate" intercept 1 treatment 1 0 / exp ;

ESTIMATE "Placebo rate" intercept 1 treatment 0 1 / exp ;

ESTIMATE "Selexipag versus Placebo" intercept 0 treatment 1 -1 / exp ;

RUN;

"ltime" is the logarithm of the time (subject years) from randomization up to min (EOS, EOMOP).

Nevent represents the annualized rate of hospitalization for a subject

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

The primary efficacy endpoint of the study is the ratio of Week 26 to baseline PVR. The design of the study is group sequential with an interim analysis allowing the trial to be stopped for futility (non-binding).

The interim analysis will be conducted at information time 0.33 [see Section 9.1]. A Pocock-type alpha spending function is used to preserve an overall type I error rate of 5% and a power of 90% for an assumed treatment group difference of –0.223 in PVR on a log scale and a standard deviation of 0.5 on the log scale [D-18.392, section 11.5].

At the interim analysis, the trial can be stopped for futility if a p-value of 0.706 or greater is observed, equivalent to a treatment group difference of 0.042 or lower on the log scale. The futility boundary is non-binding.

The overall type I error rate is preserved at 5%. See also Section 10.1.1.

The order of hierarchical testing is modified as compared to the protocol. This change is performed following interaction with the FDA (TC on 2 November 2017 [see Section 4.1]). The following endpoints will be tested in a hierarchical manner:

1. Primary efficacy endpoint
2. Change from baseline to Week 26 in 6MWD
3. Change from baseline to Week 26 in NT-proBNP.
4. Time from randomization to first disease progression event up to EOMOP + 7 days
5. Absence of worsening from baseline to Week 26 in WHO FC

10.1.1 Type I error adjustment

The interim analysis (non-binding) can only stop the trial for futility. It is not allowed to stop the trial for proof of efficacy.

At the final analysis, the overall type I error rate will be preserved over the hierarchy of endpoints as long as all p-values of the previous tests in the hierarchy are smaller than the significance level (< 0.05). If a test in the hierarchy fails to reject H_0, all subsequent tests fail as well, regardless of the size of the p-value.

10.1.2 Type II error (power)

Assuming a treatment group difference of –0.223 in change from baseline to Week 26 in log PVR and a standard deviation of 0.5, the sample size was increased from 212 subjects (in a scenario without interim analysis) to 238 to maintain 90% power for the final analysis.

10.2 General rules for data presentations

10.2.1 General guidelines for table contents

Summary statistics for continuous variables include number of non-missing observations (n), mean, standard deviation (SD), standard error of the mean (SEM), median, first and third quartiles, minimum and maximum. For discrete variables, the number of patients in the respective category and the relative frequency (percentage) are shown. Missing values are shown as a separate category and included in the computation of percentages. Percentages are shown with one decimal place.

All summaries are presented by treatment arm in the respective population. Patient disposition, demographics, baseline characteristics and exposure summaries are presented with a ‘Total’ treatment column to convey a summary of the total population assessed in this study.

Summaries of continuous variables are 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 SD. P-values are presented with four decimals. P-values smaller than 0.0001 are presented as ‘< 0.0001’.

Individual patient listings are ordered by site, treatment arm, patient number and assessment date.

Time-to-event variables are conducted on study days as time variable. KM estimates are expressed in summary tables as a fraction of 1.

10.2.2 General guidelines for table layout and formats

Treatment groups are labeled 'Selexipag' and 'Placebo' respectively. The order of the treatment groups is 'Selexipag' first, then 'Placebo', then 'Total', if applicable.

If categories on a nominal scale are displayed (such as reasons for premature discontinuation, AE PTs, etc.), the categories are sorted in descending total order. For example, a table displaying the incidence of treatment-emergent AEs by SOC and PT is sorted by descending total for the SOCs and then sorted by descending total of PTs within SOCs.

The guidelines in the Biostatistics Standards document of the Actelion Standardization Project Standard Outputs are followed.

10.2.3 Analysis of variables between EOMOP and EOT

The main analyses will be done at the Week 26 visit. After the last subject has completed the Week 26 assessment, the EOMOP will be declared, each subject will undergo EOMOP assessments, the study will be unblinded and all subjects will undergo EOT/EOS assessments. The main analysis will cover data up to Week 26. Efficacy summaries (unless otherwise specified) will include all data up to EOMOP; efficacy data collected after EOMOP will be listed. Safety summaries will include all data up to EOMOP and separately specific summaries will include all data up to EOT/EOS (these summaries are identified in the list of outputs Section 13).

10.3 Display of subject disposition, protocol deviations and analysis sets

10.3.1 Subject disposition

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

- Number of subjects screened for inclusion and reason for screen failures
- Number of subjects randomized
- Number of subjects treated with each of the three medication (macitentan, tadalafil, selexipag/placebo)
- Number of subjects who discontinued each of the three study medications up to EOMOP and separately overall (i.e., up to study closure). A patient completed treatment up to EOMOP if study medication was not discontinued during study or discontinuation occurred after the EOMOP visit
- Reasons for each of the three study treatment discontinuations
- Number of subjects who completed the study

- Reasons for study discontinuations

10.3.2 Protocol deviations

The number and percentage of subjects with major PDs leading to exclusion from any analysis set will be summarized by category (overall and by country), as defined in Section 6, on the FAS. All PDs up to EOMOP will be summarized. Important PDs (i.e., major PDs) up to EOMOP will be summarized separately. All PDs will be listed and major PDs flagged. PDs occurring from EOMOP until EOS will be listed.

10.3.3 Analysis sets

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

10.4 Analyses of subject characteristics

Subject characteristics will be summarized for the FAS, mFAS and the PPS.

10.4.1 Demographics

Demographics as described in Section 5.2.1 will be summarized. Age is analyzed as a continuous variable and as a categorical variable with categories < 18, 18–64, and ≥ 65 years. Regions (randomization strata) are North America versus rest of the world, with countries as sub-categories.

10.4.2 Baseline disease characteristics

Etiology of PAH, time since PAH diagnosis, as well as baseline WHO FC will be summarized. WHO FC will be summarized also with categories I/II and III/IV combined (randomization strata).

PVR (as reported by the investigator in the eCRF and re-calculated for analysis) as well as other parameters from the baseline RHC will be summarized.

10.4.3 Other baseline characteristics

6MWD, Borg dyspnea score, and baseline vital signs will be summarized as continuous variables.

Results from the physical examination will be listed.

10.4.4 Medical history

Medical history ongoing at the screening visit will be summarized by MedDRA SOC and PT. A second summary will be prepared by MedDRA PT only.

All clinically significant diseases or medical conditions starting prior to the screening visit will be listed, regardless if ongoing at start of study or not.

10.4.5 Previous and concomitant therapies

For study reporting purposes, all previous and study-concomitant therapies will be reported in the subject listings.

Baseline concomitant and study-treatment concomitant therapies will be summarized by therapeutic organ class and PT up to EOMOP and overall. A second summary will be prepared by PT only.

10.5 Analysis of study treatment exposure

10.5.1 Exposure

All exposure analyses will be conducted on the SAF, including all data up to EOMOP and separately for the overall treatment period.

10.5.1.1 Exposure to macitentan (days)

Exposure to macitentan in days will be summarized descriptively. Furthermore, the number and percentage of subjects being exposed at least 1, 15, 30, 60, 90, 180, 270, 365, 548, 730, and 913 days will be given in categories.

10.5.1.2 Exposure to tadalafil (days)

Exposure to tadalafil in days, regardless of dose, will be summarized descriptively. Furthermore, the number and percentage of subjects being exposed at least 1, 15, 30, 60, 90, 180, 270, 365, 548, 730, and 913 days will be given in categories.

10.5.1.3 Exposure to selexipag/placebo (days)

Exposure to selexipag/placebo in days, regardless of dose, will be summarized descriptively. Furthermore, the number and percentage of subjects being exposed at least 1, 15, 30, 60, 90, 180, 270, 365, 548, 730, and 913 days will be given in categories.

Exposure will be summarized graphically as inverse cumulative distribution function.

The maximum and weighted-average selexipag dose (b.i.d) will be summarized as a continuous variable for

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

The selexipag/placebo MTD and IMD will be summarized presenting the number and percentage of subjects with each dose level. Selexipag/placebo MTD and IMD will be also summarized as a continuous variable.

10.5.1.4 Exposure to combinations (days)

Concomitant exposure to “At least macitentan + tadalafil” and “At least macitentan + tadalafil + selexipag/placebo” in days, regardless of dose, will be summarized

descriptively. Furthermore, the number and percentage of subjects being exposed at least 1, 15, 30, 60, 90, 180, 270, 365, 548, 730, and 913 days will be given in categories.

10.5.2 Study treatment discontinuation

The reason for premature discontinuation of each treatment will be summarized separately for each of the three study medications in a similar fashion as for the subject disposition.

10.6 Analyses of the primary and secondary efficacy variables

10.6.1 Description of the estimand for the primary and first secondary efficacy variables

This section describes the estimands for primary and first secondary variables (PVR and 6MWD respectively).

Table 2 Description of the estimand for primary efficacy endpoint (ratio of Week 26 to baseline PVR)*

A) Population: All randomized patients (FAS) from targeted population, defined through protocol inclusion/exclusion criteria
B) Variable: Ratio of Week 26 to baseline PVR
C) Intercurrent events and strategies: See below description for main estimator and sensitivity estimators
D) Population-level summary measure: Ratio of geometric means (triple over dual therapy) for ratio of Week 26 to baseline PVR

Estimators	**Details of planned analyses and handling of intercurrent events**
Main estimator	**Handling of intercurrent events:** • Discontinuation of treatment from either macitentan, tadalafil or selexipag/placebo: treatment-policy strategy; all post-treatment data are used. • Death: hypothetical strategy; LOCF • Study discontinuation for other reason than death: hypothetical strategy; LOCF LOCF corresponds to BOCF if no post-baseline assessment available: PVR is measured at baseline and Week 26 [Section 10.6.2.2]. **Analysis:** Change from baseline to Week 26 in log PVR is analyzed using an ANCOVA model with treatment arm and stratification variables as factors and baseline log PVR as covariate. Ratio of geometric means (triple over dual therapy) is obtained by exponentiation [see Section 9.2].
Sensitivity estimator#1	**Handling of intercurrent events:** • Discontinuation of treatment from either macitentan, tadalafil or selexipag/placebo: treatment-policy strategy; all post-treatment data are used. • Death: hypothetical strategy; Week 26 is imputed using the largest ratio of baseline at Week 26 (largest worsening) in all subjects in the same treatment group and analysis set, such that this value is multiplied by the subject's baseline to obtain the imputed Week 26 value. • Study discontinuation for other reason than death: hypothetical strategy; if the subject is alive up to the Week 26 assessment and does not have a post-baseline value, then the median of the ratio of baseline at Week 26 from all subjects in the same treatment group and analysis set will be used to impute the Week 26 value, such that this value is multiplied by the subject's baseline to obtain the imputed Week 26 value [see Section 10.6.2.4]. LOCF is used in case the patient is alive and has a post-baseline value before Week 26. **Analysis:** Same as for main estimator.
Sensitivity estimator#2	**Handling of intercurrent events:** Multiple imputation methodology, with missing at random assumptions for intercurrent events leading to missing Week 26 assessment [see Section 9.8]. **Analysis:** Same as for main estimator performed on each imputed complete dataset, and treatment effect is summarized using the Rubin's rule [see Section 9.8].

Sensitivity estimator#3	**Handling of intercurrent events:** Same as for main estimator. **Analysis:** Same as for main estimator but without stratification variables as factors.
Sensitivity estimator#4	**Handling of intercurrent events:** • Discontinuation of treatment from either macitentan, tadalafil or selexipag/placebo: treatment-policy strategy; all post-treatment data are used. • Death: hypothetical strategy; LOCF. • Study discontinuation for other reason than death: hypothetical strategy; LOCF. • Administration of prostanoids rescue medication: All PVR assessments performed before administration of prostanoids rescue medication are used, then LOCF is applied. **Analysis:** Same as for main estimator.

*Supportive analyses will be performed by running main estimator analysis on the Per-protocol analysis set (PPS; FAS patients without any major protocol deviations leading to exclusion from PPS [see Section 7.1.4]), on modified FAS (FAS patients who received at least one dose of each of the three study treatments [see Section 7.1.3]), on modified FAS with restrictions (modified FAS patients who received all three study treatments at least until the Week 26 assessments [see Section 10.6.2.4]) and on FAS without any imputation (analysis performed on observed data).

ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; FAS = Full analysis set; LOCF = last observation carried forward; PPS = Per-protocol analysis set; PVR = pulmonary vascular resistance.

Table 3 Description of the estimand for first secondary efficacy endpoint (Change from baseline to Week 26 in 6MWD)*

A) Population: All randomized patients (FAS) from targeted population, defined through protocol inclusion/exclusion criteria
B) Variable: Change from baseline to Week 26 in 6MWD
C) Intercurrent events and strategies: See below description for main estimator and sensitivity estimators
D) Population-level summary measure: Difference in means (triple minus dual therapy) for change from baseline to Week 26 in 6MWD

Estimators	**Details of planned analyses and handling of intercurrent events**
Main estimator	**Handling of intercurrent events:** • Discontinuation of treatment from either macitentan, tadalafil or selexipag/placebo: treatment-policy strategy; all post-treatment data are used. • Death: hypothetical strategy; LOCF • Study discontinuation for other reason than death: hypothetical strategy; LOCF LOCF corresponds to BOCF if no post-baseline assessment available: 6MWD is measured at baseline, Week 12 and Week 26 [Section 10.6.4.1]. **Analysis:** Change from baseline to Week 26 in 6MWD is analyzed using an ANCOVA model with treatment arm and stratification variables as factors and baseline 6MWD as covariate [see Section 10.6.4.1].
Sensitivity estimator#1	**Handling of intercurrent events:** • Discontinuation of treatment from either macitentan, tadalafil or selexipag/placebo: treatment-policy strategy; all post-treatment data are used. • Death: hypothetical strategy; the Week 26 assessment is imputed by 0 meter. • Study discontinuation for other reason than death: hypothetical strategy; LOCF **Analysis:** Same as for main estimator.
Sensitivity estimator#2	**Handling of intercurrent events:** Multiple imputation methodology, with missing at random assumptions for intercurrent events leading to missing Week 26 assessment [see Section 9.8]. **Analysis:** Same as for main estimator performed on each imputed complete dataset, and treatment effect summarized using the Rubin's rule [see Section 9.8].
Sensitivity estimator#3	**Handling of intercurrent events:** Same as for main estimator. **Analysis:** Same as for main estimator, but without stratification variables as factors.
Sensitivity estimator#4	**Handling of intercurrent events:** Same as for main estimator. **Analysis:** MMRM to also consider Week 12 assessment in model to compute population-level summary measure [see Section 10.6.4.1].

Sensitivity estimator#5	**Handling of intercurrent events:** • Discontinuation of treatment from either macitentan, tadalafil or selexipag/placebo: treatment-policy strategy; all post-treatment data are used. • Death: hypothetical strategy; LOCF. • Study discontinuation for other reason than death: hypothetical strategy; LOCF. • Administration of prostanoids rescue medication: All 6MWD assessments performed before administration of prostanoids rescue medication are used, then LOCF is applied. **Analysis:** Same as for main estimator.

*Supportive analyses will be performed by running main estimator analysis on the Per-protocol analysis set (PPS; FAS patients without any major protocol deviations leading to exclusion from PPS [see Section 7.1.4]), on modified FAS (FAS patients who received at least one dose of each of the three study treatments [see Section 7.1.3]), on modified FAS with restrictions (modified FAS patients who received all three study treatments at least until the Week 26 assessments [see Section 10.6.3]) and on FAS without any imputation (analysis performed on observed data).

6MWD = six-minute walk distance; ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; FAS = Full analysis set; LOCF = last observation carried forward; MMRM = mixed model repeated measures analyses (PPS = Per-protocol analysis set; PVR = pulmonary vascular resistance.

10.6.2 Analysis of the primary efficacy variable(s)

The primary efficacy variable is the ratio of Week 26 to baseline PVR (Week 26 divided by baseline). PVR will be summarized descriptively at baseline and Week 26 together with its change from baseline and its ratio of baseline for the FAS, mFAS and PPS.

Change from baseline on the log-transformed PVR values will be analyzed using an ANCOVA model [see Section 9.2].

10.6.2.1 Hypothesis and statistical model

For inferential analysis, ratio of Week 26 to baseline PVR is log-transformed, as log-transformed ratios follow a normal distribution more closely. In addition, the mean change from baseline to Week 26 on log scale can be transformed into a geometric mean ratio (GMR) of Week 26 to baseline PVR.

The null hypothesis (H_0) is that the GMR of Week 26 to baseline PVR is equal in the dual and triple therapy groups. The alternative hypothesis (H_1) is that these GMRs are different, with a difference of –0.223 expressed on a log scale (triple therapy minus dual therapy).

If the GMR of Week 26 to baseline PVR in the triple therapy group is statistically significantly lower than in the dual therapy group, then triple therapy is considered superior to dual therapy.

10.6.2.2 Primary endpoint PVR

The following imputation is based on the clinical assumption that study treatment does not affect PCWP/LVEDP.

If PVR cannot be calculated due to missing PCWP/LVEDP but mPAP and CO are available for the same visit, one of the following is applied:

1. If PCWP/LVEDP is missing both at baseline and post-baseline, the treatment group medians is imputed (based on the FAS).
2. If PCWP/LVEDP is missing either at baseline or at post-baseline, the patient's available PCWP/LVEDP is imputed.

- *Baseline:* If, after this PCWP/LVEDP imputation, baseline PVR cannot still be computed for a patient, this patient is excluded from the analyses.
- *Post-baseline:* For subjects with a post-baseline PVR measurement obtained before Week 26, the (last) post-baseline PVR measurement is carried forward. For subjects without a post-baseline PVR measurement, the baseline PVR is carried forward (i.e., the ratio of Week 26 to baseline set to one).

10.6.2.3 Main analysis

The main analysis will be the analysis of the primary efficacy endpoint [see Section 5.5.1] using the algorithm described in Section 9.2 on the FAS.

For subjects with a post-baseline PVR measurement obtained before Week 26, the (last) post-baseline PVR measurement will be carried forward. For subjects without a post-baseline PVR measurement, the baseline PVR will be carried forward (i.e., the ratio of Week 26 to baseline set to one). Subjects with missing baseline PVR measurement will be excluded from analysis.

Since subjects are treated with two or three PAH medications, their PVR is expected to decrease. Subjects that do not complete 26 weeks of treatment will generally have less decrease in PVR as compared to subjects that complete 26 weeks of treatment. On a subject level, the LOCF approach is expected to be conservative.

10.6.2.4 Supportive/sensitivity analyses

The main analysis will be repeated on the primary endpoint using the mFAS (if at least 5% different from the FAS) and PPS as a supportive/sensitivity analysis.

An additional sensitivity analysis will be run on the patients in the mFAS who received all three required study treatments at least until the Week 26 assessments.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- In patients with a post-baseline PVR measurement obtained before Week 26, the post-baseline PVR measurement will be carried forward. This imputation will be performed unless one of the following occurs:
  - If a subject dies without a prior Week 26 PVR assessment, then the Week 26 PVR is imputed using the largest (worst value) ratio of baseline PVR at Week 26 in all subjects in the same treatment group and analysis set, such that this value is multiplied by the subject's baseline PVR to obtain the imputed Week 26 value.
  - If the subject is alive up to the Week 26 PVR assessment and does not have a post-baseline value, then the median of the ratio of baseline PVR at Week 26 from all subjects in the same treatment group and analysis set will be used to impute the Week 26 PVR value, such that this value is multiplied by the subject's baseline PVR to obtain the imputed Week 26 value.
- An analysis applying main ANCOVA without any imputation described in Section 10.6.2.2 (observed cases).
- An analysis on change from baseline to Week 26 (main ANCOVA analysis without PVR log-transformation)
- An analysis applying main ANCOVA without stratification factors
- To assess the robustness of the model towards possible treatment-arm-related drop-out patterns, a multiple imputations analysis for the primary endpoint will be conducted: Each missing value is replaced by a set of plausible values that represent the uncertainty about the right value to impute. Each one of the multiply imputed data

sets is analyzed then by using the same model as for the primary analysis, and the results are displayed [see Section 9.8].

- To include the intercurrent event 'administration of rescue therapy', the Week 26 PVR values of subjects who received a prostanoids pulmonary hypertension (PH) therapy (as defined in Table 9 of Section 11.5) prior to PVR assessment at Week 26 will be imputed using LOCF (including baseline) of the value prior to prostanoids PH therapy initiation (i.e., values obtained after or on prostanoids PH therapy initiation date are considered as missing). In subjects who did not receive prostanoids PH therapy prior to Week 26 PVR assessment, the same imputation rules as in the main analysis are used.

In addition, the change from baseline in PVR at Week 26 versus baseline PVR is displayed in a scatter plot. Imputed values are flagged.

10.6.2.5 Subgroup analyses

Descriptive summaries will be repeated for the individual randomization strata (North America versus rest of the world and WHO FC I/II versus WHO FC III/IV), and also for age (64 or lower versus ≥ 65 years), gender and PAH etiology (idiopathic PAH, heritable PAH, drug- or toxin-induced PAH, PAH associated with CTD, PAH associated with Others). The main ANCOVA analysis on the FAS will be also repeated on subgroups. Subgroups will be shown on a forest plot and will display estimates, 95% CI and p-value for treatment by subgroup interaction.

10.6.3 Analysis of the secondary efficacy variables

To control for multiplicity across the primary and selected secondary efficacy endpoints, statistical analyses for secondary endpoints will be performed in the following sequence:

1. Change from baseline to Week 26 in 6MWD
2. Change from baseline to Week 26 in NT-proBNP
3. Time from randomization to first disease progression event up to EOMOP + 7 days
4. Absence of worsening from baseline to Week 26 in WHO FC

The changes from baseline to Week 26 in other RHC variables will be excluded from this hierarchical testing strategy as they include too many variables. Secondary efficacy variables will be analyzed at $\alpha = 0.05$ (two-sided).

All analyses for secondary efficacy variables are presented on the FAS, mFAS (if at least 5% different from the FAS) and PPS.

An additional sensitivity analysis is run on the patients in the mFAS who received all three required study treatments at least until the Week 26 assessments.

10.6.4 Secondary endpoints

10.6.4.1 Change from baseline to Week 26 in six-minute walk distance

6MWD will be summarized by a scheduled analysis time window [see Table 5].

Change from baseline to Week 26 in 6MWD will be analyzed using an ANCOVA model with factors for treatment arm and stratification factors (region, WHO FC) and baseline 6MWD as a covariate, as described Section 9.3.

For the main analysis, in case of a missing Week 26 assessment, for subjects with a post-baseline 6MWD measurement obtained before Week 26, the (last) post-baseline 6MWD measurement will be carried forward. For subjects without a post-baseline 6MWD measurement, the baseline 6MWD will be carried forward. Patients without a baseline value will be excluded from analysis.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- In patients with a post-baseline 6MWD measurement obtained before Week 26, the post-baseline 6MWD measurement will be carried forward. This imputation will be performed unless the following occurs:
  - If a subject dies without a prior Week 26 6MWD assessment, then the Week 26 6MWD is imputed by 0 meter.
- An analysis applying main ANCOVA without any imputation of missing Week 26 assessments (observed cases).
- An analysis applying main ANCOVA without stratification factors
- To assess the robustness of the model towards possible treatment-arm-related drop-out patterns, a multiple imputations analysis will be conducted: each missing value is replaced by a set of plausible values that represent the uncertainty about the right value to impute. Each one of the multiply imputed data sets is analyzed then by using the same model as the main analysis, and the results are displayed [see Section 9.8].
- An MMRM done on the FAS after LOCF imputation for missing Week 12/Week 26 assessments [see Section 9.6].
- To include the intercurrent event ‘administration of rescue therapy’, the Week 26 6MWD values of subjects who received prostanoids PH therapy (as defined in Table 9 of Section 11.5) prior to 6MWD assessment at Week 26 will be imputed using LOCF (including baseline) of the value prior to prostanoids PH therapy initiation (i.e., values obtained after or on prostanoids PH therapy initiation date are considered as missing). In subjects who did not receive prostanoids PH therapy prior to Week 26 6MWD assessment, the same imputation rules as in the main analysis are used.

10.6.4.2 Change from baseline to Week 26 in NT-proBNP

NT-proBNP will be summarized by scheduled analysis time window [see Table 5].

NT-proBNP values are log-transformed (base e) and change from baseline to Week 26 in log-transformed NT-proBNP will be analyzed using an ANCOVA model with factors for treatment arm and stratification factors (region, WHO FC) and baseline log-transformed NT-proBNP as a covariate.

For display, point estimates and bounds of the 95% confidence intervals are exponentiated, yielding a GMR similar to the primary endpoint analysis.

For the main analysis, in case of a missing Week 26 assessment, for subjects with a post-baseline NT-proBNP measurement obtained before Week 26, the (last) post-baseline NT-proBNP measurement is carried forward. For subjects without a post-baseline NT-proBNP measurement, the baseline NT-proBNP is carried forward. Patients without baseline value will be excluded from analysis.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- In patients with a post-baseline NT-proBNP measurement obtained before Week 26, the post-baseline NT-proBNP measurement will be carried forward. This imputation will be performed unless one of the following occurs:
  - If a subject dies without a prior Week 26 NT-proBNP assessment, then the Week 26 NT-proBNP is imputed using the largest ratio of baseline NT-proBNP at Week 26 in all subjects in the same treatment group and analysis set, such that this value is multiplied by the subject's baseline NT-proBNP to obtain the imputed Week 26 value.
  - If the subject is alive up to the Week 26 NT-proBNP assessment and does not have a post-baseline value then the median of the ratio of baseline NT-proBNP at Week 26 from all subjects in the same treatment group and analysis set will be used to impute the Week 26 NT-proBNP value, such that this value is multiplied by the subject's baseline NT-proBNP to obtain the imputed Week 26 value.
- An analysis applying main ANCOVA without any imputation of missing Week 26 assessments (observed cases).

10.6.4.3 Time to the first disease progression event

The time from randomization to the first disease progression event up to EOMOP + 7 days will be analyzed using KM estimates and KM plots, as described in Section 9.5.

Patients will be censored at min (EOS, EOMOP + 7) days for the main analysis (FAS).

A log rank test for treatment difference will be computed, stratified by randomization strata (region and WHO FC at baseline). Additionally, a Cox regression model will be fitted using region (North America versus rest of the world) and WHO FC at baseline as factors.

The components of the first occurrence of disease progression events will be tabulated. If for a given subject two components occur on the same day then the worst is tabulated

according to the hierarchy stated in Section 5.5.2.5: death, hospitalization, initiation of therapy for worsening PAH, and clinical worsening.

For sensitivity analyses, patients will be censored at EOMOP + 7 days or day of last drug intake of any of the three study medications + 7 days, whichever is the earliest (sensitivity analysis #1, FAS); at EOMOP + 7 days or end of double-blind study treatment + 7 days, whichever is the earliest (sensitivity analysis #2, restricted to patients in the FAS who received at least one dose of double-blind study treatment); and at EOS (sensitivity analysis #3, FAS).

10.6.4.4 Absence of worsening from baseline to Week 26 in WHO FC

The absence of worsening of WHO FC from baseline to Week 26 will be summarized as a categorical variable and analyzed using a logistic regression model, as described in Section 9.4. The main analysis will be restricted to patients with WHO FC I–III at baseline (using the definition in Section 5.5.2.3.1), and a sensitivity analysis will be performed including all patients (also those with WHO FC IV at baseline using the definition of Section 5.5.2.3.2).

In case of a missing Week 26 assessment, for subjects with a post-baseline WHO FC measurement obtained before Week 26, the (last) post-baseline WHO FC measurement will be carried forward. For subjects without a post-baseline WHO FC measurement, the baseline WHO FC will be carried forward. Patients without baseline value will be excluded from analysis.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- In patients with a post-baseline WHO FC measurement obtained before Week 26, the post-baseline WHO FC measurement will be carried forward. This imputation will be performed unless the following occurs:
  - If a subject dies without prior Week 26 WHO FC assessment, then the Week 26 WHO FC is imputed by class IV.
- An analysis without any imputation of missing Week 26 assessments (observed cases).

WHO FC at baseline and at Week 26 will also be displayed in a shift table, using the same imputation rules as for the main analysis.

10.6.4.5 Change from baseline to Week 26 in hemodynamic variables other than PVR

The change from baseline to Week 26 in variables from RHC other than PVR (mPAP, CI, TPR, mRAP, venous oxygen saturation) will be summarized on the FAS. Analysis will be performed after LOCF imputation and repeated without imputation (observed cases).

The change from baseline to Week 26 in RHC parameters other than PVR will be analyzed on the FAS using an ANCOVA model with factors for treatment arm and stratification

factors (region, WHO FC) and respective baseline value as covariate, as described in Section 9.3.

10.6.4.6 Analyses of endpoints after Week 26, EOMOP and EOT visits

Due to the design of the study, EOMOP for all subjects will be announced once the last subject has been enrolled, i.e., approximately 26 weeks in advance; all subjects will undergo the EOMOP visit. The study will be unblinded shortly after the last subject's EOMOP visit.

All summaries and statistical models will use data up to EOMOP or EOMOP + 7 as stated. Assessments made after the period will be listed only.

10.6.4.7 Subgroup analyses

Descriptive summaries will be repeated on the FAS for 6MWD for the individual randomization strata (North America versus rest of the world and WHO FC I/II versus WHO FC III/IV), age (64 or lower versus ≥ 65 years), gender, and PAH etiology (idiopathic PAH, heritable PAH, drug- or toxin-induced PAH, PAH associated with CTD, PAH associated with Others).

The main 6MWD ANCOVA analysis on the FAS will be also repeated on subgroups. In addition, subgroups will be shown on a forest plot and will display estimates, 95% CI and p-value for treatment by subgroup interaction added in the model.

10.7 Analysis of other efficacy variables

All analyses for other efficacy variables will be presented on the FAS.

Patient data up to EOMOP (for visit-based data) or EOMOP + 7 days (for time-to-event data), respectively, will be used for summaries and analyses. Assessments collected after EOMOP will be listed. Sensitivity analysis up to EOS will be performed only after all patients' EOS.

10.7.1 Change of NT-proBNP from baseline to all regular collection time points up to EOMOP

NT-proBNP will be log transformed (base e). Changes from baseline to Week 26 in log-transformed values will be analyzed using the MMRM model, as described in Section 9.6. Note that log-transformed baseline NT-proBNP will be used as a covariate. Treatment contrasts and the corresponding 95% confidence intervals will be computed for each regular collection visit up to Week 26. The treatment differences and confidence interval boundaries are exponentiated and will be thus displaying a GMR. Data after Week 26 will be reported with descriptive statistics only.

10.7.2 Change of 6MWD from baseline to all regular collection time points up to EOMOP

Changes from baseline to Week 26 in 6MWD will be analyzed in an MMRM model, as described in Section 9.6 (also described as sensitivity analysis for 6MWD secondary endpoint). Baseline 6MWD will be used as the continuous covariate. Treatment contrasts and the corresponding 95% confidence intervals will be computed for each regular visit where 6MWD was collected up to Week 26. Data after Week 26 will be reported with descriptive statistics only.

10.7.3 Absence of worsening from baseline in WHO FC to all regular collection time points up to EOMOP

The absence of worsening of WHO FC to all scheduled study visits where WHO FC is assessed up to EOMOP will be summarized as a categorical variable for patients in WHO FC I–III at baseline using the definition of Section 5.5.2.3.1.

Subjects in WHO FC IV at baseline will be excluded from the analysis. A sensitivity analysis will be performed including subjects in WHO FC IV at baseline (for whom worsening is defined as death or hospitalization due to PAH), as described in Section 5.5.2.3.2.

10.7.4 Unsatisfactory clinical response

Unsatisfactory clinical response will be summarized for all regular visits from Week 26 onwards. The number and percentage of patients with unsatisfactory response will be displayed along with the - criteria for unsatisfactory response for each visit up to EOMOP.

Patients fulfilling one or more unsatisfactory response criteria at baseline will be also included in the analysis.

10.7.5 Number of treatment goals met at Week 26

The number of treatment goals met will be summarized at Week 26 for all three definitions of the number of treatment goals met [see Section 5.5.3.3] along with the number of patients who met each individual treatment goal. The summary will be done both ways, considering the number of treatment goals as a continuous and a categorical variable.

The number of treatment goals met will be tested for treatment arm difference using a CMH test adjusting for baseline WHO FC (randomization stratum) and baseline 6MWD ($\leq$ 440 m vs > 440 m).

The number of treatment goals at baseline and at Week 26 will also be summarized as a shift table.

10.7.6 Improvement of WHO FC from baseline to Week 26

The improvement of WHO FC from baseline to Week 26 will be summarized as a categorical variable and analyzed using a logistic regression model, as described in

Section 9.4. The main analysis will be restricted to patients with WHO FC II–IV at baseline (using the definition in Section 5.5.3.3). In case of a missing Week 26 assessment, for subjects with a post-baseline WHO FC measurement obtained before Week 26, the (last) post-baseline WHO FC measurement will be carried forward. For subjects without a post-baseline WHO FC measurement, the baseline WHO FC will be carried forward. Patients without baseline value will be excluded from analysis.

10.7.7 Hospitalizations up to EOMOP

All hospitalization data will be listed.

10.7.7.1 Time from randomization to first hospitalization (all causes) up to EOMOP

The time from randomization to the first hospitalization (all causes) up to EOMOP will be analyzed using KM estimates and KM plots, as described in Section 9.5.

A log rank test for treatment difference will be computed without stratification variables and a Cox regression model will be fitted without stratification variables.

10.7.7.2 Time from randomization to first hospitalization for worsening PAH up to EOMOP

The time from randomization to the first hospitalization for worsening PAH up to EOMOP will be analyzed using KM estimates and KM plots, as described in Section 9.5.

A log rank test for treatment difference will be computed without stratification variables and a Cox regression model will be fitted without stratification variables.

10.7.7.3 Annualized rate of hospitalization (all causes) up to EOMOP

The annualized rate of hospitalization (all causes) up to EOMOP will be summarized descriptively. In addition, a Poisson regression model as described in Section 9.9 will be used for exploratory statistical analysis.

10.7.7.4 Annualized rate of hospitalization for worsening PAH up to EOMOP

The annualized rate of hospitalization for worsening PAH up to EOMOP will be summarized descriptively. In addition, a Poisson regression model as described in Section 9.9 will be used for exploratory statistical analysis.

10.7.7.5 Annualized rate of days spent in hospital (all causes) up to EOMOP

The annualized rate of days spent in hospital (all causes) up to EOMOP will be summarized using descriptive statistics.

10.7.7.6 Annualized rate of days spent in hospital for worsening PAH up to EOMOP

The annualized rate of days spent in hospital for worsening PAH up to EOMOP will be summarized using descriptive statistics.

10.8 Analysis of safety variables

This section describes the analyses of the safety variables defined in Section 5.6. All analyses of safety variables will be based on the SAF. Safety analyses specific to one study medication (e.g., treatment-emergent AEs related to macitentan) will be restricted to the subset of subjects from the SAF who received at least one dose of the corresponding study medication.

10.8.1 Adverse events

All AEs captured from signature of informed consent up to EOS will be reported in the subject listings.

All AEs will be coded using the MedDRA dictionary valid at the time of database closure.

In general, AEs will be summarized 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 (PT). A second summary will present a summary of each individual AE at the PT level.

The following summaries will be provided for AEs

- Incidence of AEs from informed consent signature until initiation of first study drug (Day −1)
- Incidence of treatment-emergent AEs up to EOMOP and separately for the overall study period
- Incidence of treatment-emergent AEs related to each of the three study medications, separately for each study medication up to EOMOP and separately for the overall study period
- Incidence of treatment-emergent AEs by maximum intensity (summary only at the PT level) up to EOMOP
- Incidence of treatment-emergent AEs leading to discontinuation of each of the three study medications, separately for each study medication up to EOMOP and separately for the overall study period.

A table of the most frequent PTs (incidence rate of at least 5% in any treatment arm) up to EOMOP.

Additionally, the incidence of AEs will be analyzed for the following time periods

- AEs with onset between Day 1 until EOMOP (or EOS whichever is earlier)
- AEs with onset between Day 1 and before start of double-blind treatment (selexipag/placebo). For subjects who did not receive double-blind treatment, AEs with onset between Day 1 and Day 14 (included) will be displayed
- AEs with onset between first and last day (+ 30 days) of macitentan treatment (or EOMOP, whichever is earlier)

- AEs with onset between first and last day (+ 30 days) of tadalafil treatment (or EOMOP, whichever is earlier)
- AEs with onset between first and last day (+ 30 days) of double-blind treatment (or EOMOP, whichever is earlier)
- AEs with onset between EOMOP and EOT + 30 days. The summary will be restricted to subset of subjects from the SAF with ongoing treatment at time of EOMOP visit.
- AEs with onset after EOT (30 day safety follow-up)
- AEs with onset during the titration period of double-blind treatment versus AEs with onset during the maintenance period of double-blind treatment (up to last day in the maintenance period or EOMOP, whichever is earlier)
- AEs with onset between first and last day (+ 3 days) of double-blind treatment (or EOMOP, whichever is earlier).

10.8.2 Deaths, other serious adverse events

10.8.2.1 Death

Study deaths will be summarized by SOC and PT up to EOMOP and separately for the overall study period. A listing of primary reasons for death and all AEs leading to death will be provided.

10.8.2.2 Serious adverse events

Treatment-emergent SAEs will be displayed by SOC and PT as well as by PT alone up to EOMOP and separately for the overall study period. A summary will be created for treatment-emergent SAEs related to each of the three study medications, separately.

Listings will be provided for all SAEs, SAEs prior to the first dose (i.e., first intake) of study medication, SAEs occurring more than 30 days after the last dose of study medication.

A separate summary of treatment-emergent SAEs will be provided for patients who have received at least one dose of double-blind study medication.

Listing of all SAEs with onset date after start of a new PAH specific therapy (as defined in Table 9 of Section 11.5) will be provided.

10.8.3 Other adverse event analyses

10.8.3.1 Important identified or potential risks

Important identified or potential-risk AEs treatment emergent to selexipag will be displayed by the individual category up to EOMOP.

10.8.3.2 Adverse events related to the addition of selexipag to the dual treatment regimen

Additional tables will be prepared to investigate safety signals that may be related to the addition of selexipag to the dual treatment regimen. For those tables, only AEs with onset during exposure to selexipag/placebo are tabulated:

- Incidence of AEs during selexipag/placebo exposure up to EOMOP
- Incidence of SAEs during selexipag/placebo exposure up to EOMOP
- Incidence of AEs during selexipag/placebo exposure related to selexipag/placebo up to EOMOP
- Incidence of AEs during selexipag/placebo exposure leading to discontinuation of selexipag/placebo up to EOMOP
- Incidence of AEs during selexipag/placebo exposure leading to death up to EOMOP.

10.8.3.3 Other adverse events of special interest

The incidence of treatment-emergent symptomatic hypotension AEs will be displayed by PT up to EOMOP.

The incidence of AEs typical of prostanoids treatment (as defined in Section 5.6.6) with onset date between start of double-blind treatment and last day (+ 3 days) of double-blind treatment (or EOMOP, whichever is earlier) will be displayed by PT.

10.8.3.4 Summaries of adverse events for disclosure

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and not for the purpose of the CSR), treatment-emergent (S)AEs will be summarized displaying, for each treatment group, counts and percentages of subjects with at least a treatment-emergent event plus the number of events (counted exactly the number of times they occurred also within a subject) by SOC and individual PT. The summary table will be presented in descending order according to the incidence in the selexipag treatment group (i.e., SOC and individual PT within each SOC, with the highest number of occurrences appearing first). Equal frequency of different individual PTs will be 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 up to EOMOP [see Section 10.8.2.2]
- Summary of treatment-emergent SAEs judged to be treatment related by the investigator up to EOMOP [see Section 10.8.2.2]
- Summary of treatment-emergent SAEs with fatal outcome up to EOMOP
- Summary of treatment-emergent SAEs with fatal outcome judged to be treatment (related by the investigator up to EOMOP
- Summary of non-serious AEs with an incidence of 5% or higher in any treatment group up to EOMOP.

10.8.4 Electrocardiography

ECG is not assessed in this trial.

10.8.5 Laboratory tests

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. In some cases the same sample can be assessed twice by the central laboratory. If the results are different, the highest value will be used for display in summary tables.

The data will be assigned to the most appropriate analysis time point using time windows, as described in Table 5.

Laboratory values will be summarized by visit in their respective SI unit together with the respective changes from baseline for all scheduled study visits up to EOMOP. Laboratory test assessments within 30 days of the last dose of study medication will be used for summaries.

All laboratory values will be listed.

10.8.5.1 Marked laboratory abnormalities

Actelion internal guidelines (OTH-000005) will be used for the definitions of marked abnormalities. Standard numeric laboratory variables will be transformed to standard units. All laboratory data transferred will be taken into account regardless of their correspondence to scheduled or unscheduled assessments.

Table 4 Definition of marked laboratory abnormalities

Parameter (SI unit)	LL Marked	LLL Alert	HH Marked	HHH Alert
Hemoglobin (g/L)				
baseline within ULN	< 100	< 80	> 20 above ULN	> 40 above ULN
baseline above ULN	< 100	< 80	> 20 above baseline	> 40 above baseline
Hematocrit (L/L)				
males	< 0.32	< 0.20	> 0.60	> 0.65
females	< 0.28	< 0.20	> 0.55	> 0.65
Platelets (10^9/L)	< 75	< 50	> 600	> 999
Leucocytes (10^9/L)	< 3	< 2	> 20	> 100
Neutrophils (10^9/L)	< 1.5	< 1.0	-	-
Eosinophils (10^9/L)	-	-	> 5	-
Lymphocytes (10^9/L)	< 0.8	< 0.5	> 4	> 20
ALT	-	-	> 3 ULN	> 5 ULN
AST	-	-	> 3 ULN	> 5 ULN
Alkaline Phosphatase	-	-	> 2.5 ULN	> 5 ULN
Total Bilirubin	-	-	> 2 ULN	> 5 ULN
INR	-	-	> 1.5 ULN	> 2.5 ULN
Creatinine		-		
baseline within ULN	-	-	> 1.5 ULN	> 3 ULN
baseline above ULN	-	-	> 1.5 baseline	> 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
Uric Acid (µmol/L)	-	-	> 590	> 720
Albumin	< 30	< 20	-	-
Creatinine Clearance/eGFR (mL/min)	< 60	< 30	-	-
BUN	-	-	> 2.5 ULN	> 5 ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; ULN = upper limit of normal.

The number and percentage of subjects with treatment-emergent (i.e., within 30 days of last dose) post-baseline laboratory abnormalities will be tabulated by treatment group up to EOMOP.

For subjects with laboratory abnormality at baseline, the post-baseline value will be counted as a post-baseline abnormality only if the post-baseline category is worse than the baseline category.

10.8.5.2 Other notable laboratory abnormalities (hepatic safety)

The incidence of the following notable treatment-emergent laboratory values post baseline will be tabulated up to EOMOP:

- 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)

An e-DISH plot of the maximum treatment-emergent post-baseline ALT by concomitant post-baseline bilirubin (in multiples of ULN) will be presented to detect possible cases of drug-induced liver toxicity up to EOMOP. In case of missing concomitant bilirubin (in multiples of ULN), the closest non-missing bilirubin value (in multiple of ULN) to the peak ALT value (within 14 days) will be used.

10.8.6 Vital signs and body weight

Vital signs assessments within 30 days of the last dose of study medication will be used for summaries up to EOMOP. All data, regardless if from scheduled or unscheduled visits will be used. The data will be assigned to the most appropriate analysis time point using time windows as described in Table 7.

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

10.8.6.1 Clinically relevant vital signs abnormalities

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

- Systolic blood pressure < 90 mmHg
- Diastolic blood pressure < 50 mmHg
- Decrease of > 40 mmHg in systolic blood pressure from baseline
- Decrease of > 20 mmHg in diastolic blood pressure from baseline
- All four notable criteria fulfilled

All treatment-emergent post-baseline assessments from scheduled and unscheduled visits will be used to determine notable blood pressure values.

For the first two criteria above, subjects with vital signs abnormality at baseline and post-baseline (e.g., systolic blood pressure < 90 mmHg at baseline and post-baseline) are not counted as having a post baseline abnormality.

10.9 Interim analysis

An interim analysis for futility (non-binding) will be conducted when 33% of the patients have completed their Week 26 visit or discontinued prematurely.

The unblinded analyses for IDMC closed sessions (including futility interim analysis) are performed by the ISAC according to ISAC's own analysis plan (and following stopping rules mentioned in protocol section 11.5). The study team remains blinded. The ISAC is responsible for the content of these unblinded analyses for the closed reports provided to the IDMC (see IDMC charter).

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Study treatment start and end date

The study treatments are macitentan, tadalafil and selexipag/placebo, which are scheduled to start at different time points after randomization. Each of the three study treatments may be discontinued while the other treatments are continued.

The first dose (i.e., first intake) of any of the three study treatments is considered study treatment start date.

The last dose (i.e., last intake) of any of the three study treatments is considered study treatment end date.

11.1.1 Treatment-emergent assessments or events

Treatment-emergent assessments or events are assessments made or events experienced within the next full 30 days after the last dose of study medication, i.e., if the day of the last dose is on Day x, all events up to Day x + 30 + 1 are considered treatment emergent.

11.2 Study days

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

11.3 Baseline definition

The last value prior to first dose (i.e., first intake) of study medication 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.

11.4 Assignment of assessment dates to the most appropriate analysis time point (visit windows)

To allow for unscheduled assessments and to minimize the impact of missed assessments at regular study visits, all values obtained up to 30 days after last dose of study medication are assigned the most appropriate analysis time point using a time window. All

unscheduled visits, the EOMOP and EOT visits are realigned using windowing rules, if they were within 30 days after the last dose of study drug.

Not all assessments are conducted at every study visit. Therefore, different visit windows are used for different assessments.

11.4.1 Visit windows for primary efficacy variable, hemodynamics from RHC

The primary efficacy variable, PVR, and other hemodynamic assessments are determined by RHC at screening and Week 26.

In case more than one pre-baseline RHC is obtained, the assessments from the latest RHC prior to first dose (i.e., first intake) of study are used for baseline.

In case more than one post-baseline RHC is obtained, the assessments from the RHC closest to Week 26 are used. If two assessments are equally close, the earliest of the two assessments is used.

11.4.2 Visit windows for six-minute walk test, WHO FC, NT-proBNP, regular laboratory (except hemoglobin and liver function tests)

These assessments are obtained at Week 12, Week 26 and every study visit thereafter. They are mapped to the most appropriate time point using Table 5.

Table 5 Time windows for 6-minute walk tests, WHO FC and laboratory assessments (except hemoglobin and liver function tests)

Visit label	Target Day	Lower limit of study day	Upper limit of study day
Baseline	1	Latest assessment before or at Day 1	
Week 12	84	2	133
Week 26	182	134	197
Month 12	365	198	456
Month 18	548	457	638
Month 24	730	639	821
Month 30	913	822	1003
Month 36	1095	1004	1186
…			

11.4.3 Visit windows for hemoglobin and liver function tests

These assessments are obtained monthly up to Week 26 and every study visit thereafter. They are mapped to the most appropriate time point using Table 6.

Table 6 Time windows for hemoglobin and liver function tests

Visit label	Target Day	Lower limit of study day	Upper limit of study day
Baseline	1	Latest assessment before or at Day 1	
Month 1	30	2	45
Month 2	60	46	75
Month 3	90	76	115
Month 4	120	116	135
Month 5	150	136	166
Week 26	182	167	197
Month 12	365	198	456
Month 18	548	457	638
Month 24	730	639	821
Month 30	913	822	1003
Month 36	1095	1004	1186
…			

11.4.4 Visit windows for vital signs and body weight

Vital signs assessments are mapped to the most appropriate time point using Table 7.

Table 7 Time windows for vital signs assessments

Visit label	Target Day	Lower limit of study day	Upper limit of study day
Baseline	1	Latest assessment before or at Day 1	
Day 15	15	2	50
Week 12	84	51	133
Week 26	182	134	197
Month 12	365	198	456
Month 18	548	457	638
Month 24	730	639	821
Month 30	913	822	1003
Month 36	1095	1004	1186
…			

11.5 Identification of prohibited medication and medications of special interest

The search criteria laid out in Table 8 are used to identify prohibited and special-interest drug classes.

Table 8 Clinical forbidden medications list

Drug class	Generic name/active ingredient	Rule Id (within category)	SDG Level 1	SDG Level 2	SDG Level 3	SDG Scope	Drug Name	List of ATC codes	Ingredients
Prostacyclin analogs	Epoprostenol	1							Epoprostenol
	Treprostinil	2							Treprostinil
	Iloprost	3							Iloprost
	Beraprost	4							Beraprost
Prostacyclin receptor agonist	Selexipag	1							Selexipag Ralinepag
Endothelin receptor antagonist	Bosentan	1							
	Ambrisentan	2							
	Macitentan	3							
Phosphodiesterase-5 inhibitor (PDE-5i)			Phosphodiesterase (PDE) inhibitors	Phosphodiesterase type 5 inhibitors		narrow + broad			
Soluble guanylate cyclase stimulator	Riociguat	1							Riociguat
	Nitric oxide	2							Nitric oxide
Strong inducers of CYP3A4			CYP3A interacting substances	CYP3A inducers	Strong CYP3A inducers				
Strong inhibitors of CYP3A4			CYP3A interacting substances	CYP3A inhibitors	Strong CYP3A inhibitors				
Another investigational drug		1					Investigational antineoplastic drugs		
		2					Investigational drug		
Organic nitrates		1						C01DA	

		2							Erityl tetranitrate Glyceryl trinitrate Isosorbide dinitrate Isosorbide mononitrate Methylpropyl propanediol dinitrate Organic nitrates Pentaerithrityl tetranitrate Propatylnitrate Tenitramine Trolnitrate
Doxazosin									Doxazosin
Strong CYP2C8 inhibitors			CYP2C8 interacting substances	CYP2C8 inhibitors	Strong CYP2C8 inhibitors				

The search criteria laid out in Table 9 are used to identify new PAH specific therapies.

Table 9 New PAH specific therapies

Category	**Subcategory**	**Ingredient names**
Antihypertensives for pulmonary arterial hypertension	ERAs	Ambrisentan, Bosentan
	PDE-5 Inhibitors	Sildenafil, Vardenafil, Udenafil
	sGC stimulator	Riociguat
Prostanoids		Epoprostenol, Treprostinil, Iloprost, Beraprost, selexipag
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. ERA = endothelin receptor antagonist; PDE-5 = phosphodiesterase-5; sGC = soluble guanylate cyclase.		

11.6 Handling of selexipag/placebo dose titrations over day

In the protocol [D-18.392], it is recommended that dose changes (up- or down-titration) shall be conducted over one day of 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 the same date as the start date of the new regimen. To account for the actual daily dose the following handling convention was used:

1. The end date of the old dose regimen is reduced by one day
2. The start date of the new dose regimen is increased by one day
3. A record with an intermediate dose is created for the day of dose change

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

Table 10 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	**15**Sep2016	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.

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

Missing and incomplete date and time fields should be avoided as much 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 is employed.

1. Dates are split in three parts: year, month and day. Year is the top level, month is medium level and day is low level. If a part expected to contain a number is numeric but the value is outside a valid range, the complete date is handled as missing. For example, if date = 44Nov2000 the whole date is considered to be missing.
2. If a part expected to contain a number is not numeric, i.e., contains values such as, for example, ND, NA, --, ??, 2?, it is considered as missing.
3. If a part is missing, all other parts of a lower level are considered to be missing. This means that a ddmmyy date '21ND99' is considered as '----99'.
4. Missing parts are changed 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 macitentan or tadalafil AND Medication stop date not collected or with the upper limit after the study drug start AND The treatment start day falls in the range of possible dates. In which case it is the ***study drug 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 drug start or missing AND Upper limit is after the study drug start AND Not tagged as ongoing at start of macitentan or tadalafil 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 drug, 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: 30 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

12.4 Imputation of hospital admission and discharge dates

12.4.1 Hospital admission date

Date is incomplete	Date is missing
If the onset of the AE leading to hospitalization falls in the range of possible dates, it is the onset date of the AE. In all the other cases, it is the lower limit.	The onset date of the AE leading to hospitalization.

12.4.2 Hospital discharge date

Date is incomplete	Date is missing
The upper limit	The hospitalization is considered as ongoing.

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

This section lists all outputs (i.e., listings, tables and figures) produced to display the results of the analyses defined in the sections above.

The table, listing and figure naming conventions have three components: ***Type*** (T, L, F), ***Name*** (free text, not longer than ten characters), ***Suffix*** (for example, for analysis sets, or subgroups, not longer than four characters). Multiple suffixes can be added; components/suffixes are separated by '_'.

Key deliverables are marked as being of priority. Outputs marked as '***' will be also created on blinded combined groups for IDMC open sessions.

Mock layouts refer to specifications in the AC-065A308 'Layouts for TLFs' document.

13.1 Subject disposition

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
DISP	T	Subject disposition	SCR	x***	DISP001	x
SCRF	T	Reasons for screening failure	SCR	***	DISP002	
SCRF	L	Listing of reasons for screening failure	SCR		LSTCSR011 (from standard catalog)	
PWDS	T	Reasons for premature discontinuation of study up to EOMOP	FAS	x***	DISP004	x#
ANA	T	Overview of analysis sets	FAS	x***	ANA001	
ANA-EX	T	Exclusions from analysis sets	FAS		ANA002	
RAN	L	Listing of randomization information	FAS		LSTRAN (from standard catalog)	
VIS	L	Listing of study visits	SCR		LSTVIS001	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, ***Created on blinded combined groups for IDMC open sessions, # without 'up to EOMOP' in the title

13.2 Protocol deviations

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
PD	T	Summary of protocol deviations leading to an exclusion from the Per Protocol Set	FAS	***	PD001	
PD	L	Listing of protocol deviations leading to an exclusion from the Per Protocol Set	FAS		LSTPD001	
PDALL	T	Summary of protocol deviations up to EOMOP	FAS		PD001	
PD-IMP	T	Summary of important protocol deviations up to EOMOP	FAS	x	PD001	
PD-EXC	T	Summary of protocol deviations leading to an exclusion from Per Protocol Set, by country	FAS		PD001	
PDALL	L	Listing of all protocol deviations	SCR		LSTPD001	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, ***Created on blinded combined groups for IDMC open sessions

13.3 Subject characteristics

13.3.1 Demographics

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
DEM	T	Summary of demographics	FAS, mFAS, P	x (FAS***)	DEM001
DEM	L	Listing of demographics	SCR		LSTDEM001

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, P = Per-protocol analysis set, ***Created on blinded combined groups for IDMC open sessions

13.3.2 Baseline disease characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
BAS	T	Summary of disease baseline characteristics	FAS, mFAS, P	x (FAS***)	BAS001
BAS	L	Listing of disease baseline characteristics	SCR		LSTDEM003
BAS-RHC	T	Summary of baseline values of efficacy endpoints from right-heart catheterization	FAS, mFAS, P	x (FAS***)	BAS002

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, P = Per-protocol analysis set, ***Created on blinded combined groups for IDMC open sessions

13.3.3 Other baseline characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
BAS-O	T	Summary of other baseline characteristics	FAS, mFAS, P	x (FAS***)	BAS003
PHYS	L	Listing of physical examination results	SCR	***	LSTDEM002

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, P = Per-protocol analysis set, ***Created on blinded combined groups for IDMC open sessions

13.3.4 Medical history

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
MH-SOC	T	Summary of medical history ongoing at screening visit, by primary system organ class and preferred term	FAS, mFAS	x (FAS***)	LAYMH001 (from standard catalog)
MH-PT	T	Summary of medical history ongoing at screening visit, by preferred term	FAS, mFAS		LAYMH002
MHHEP-PT	T	Summary of medical history ongoing at screening visit, by preferred term and subjects with and without post-baseline hepatic lab abnormality	FAS		LAYMH002

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
MH	L	Listing of medical history	SCR		LSTCSR043 (from standard catalog)

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, ***Created on blinded combined groups for IDMC open sessions

13.3.5 Previous and concomitant therapies

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
CM-BSL-SOC	T	Summary of therapies concomitant to baseline by Anatomical Therapeutic Chemistry (ATC) Class and Preferred Term *[Add footnote: A baseline-concomitant therapy is any treatment that is started prior to study treatment and is ongoing at Day 1.]*	FAS, mFAS	(FAS***)	LAYCMED001 (from standard catalog)	
CM-BSL-PT	T	Summary of therapies concomitant to baseline by Preferred Term *[Add footnote: A baseline-concomitant therapy is any treatment that is started prior to study treatment and is ongoing at Day 1.]*	FAS, mFAS	***	LAYCMED002	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
CM-BSLHEP-PT	T	Summary of therapies concomitant to baseline by Preferred Term and subjects with and without post-baseline hepatic lab abnormality *[Add footnote: A baseline-concomitant therapy is any treatment that is started prior to study treatment and is ongoing at Day 1.]*	FAS		LAYCMED002	
CM-SOC	T	Summary of therapies concomitant to study treatment up to EOMOP by Anatomical Therapeutic Chemistry (ATC) Class and Preferred Term	FAS, mFAS	***	LAYCMED001 (from standard catalog)	
CM-PT	T	Summary of therapies concomitant to study treatment up to EOMOP by Preferred Term	FAS, mFAS	***	LAYCMED002	
CM	L	Listing of subjects with previous and concomitant therapies	SCR		LSTCSR044 (from standard catalog)	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, ***Created on blinded combined groups for IDMC open sessions

13.4 Study treatment exposure

13.4.1 Exposure

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
EXP-M	T	Exposure to macitentan up to EOMOP	S	x***	EXP001	x#

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
EXP-M	F	Exposure to macitentan up to EOMOP	S	***	FIGLINE001 (from standard catalog)	x#
EXP-T	T	Exposure to tadalafil up to EOMOP	S	x***	EXP001	x#
EXP-T	F	Exposure to tadalafil up to EOMOP	S	***	FIGLINE001 (from standard catalog)	x#
EXP-S	T	Exposure to double-blind study treatment (selexipag/placebo) up to EOMOP	S	x***	EXP0001	x#
EXP-S	F	Exposure to double-blind study treatment (selexipag/placebo) up to EOMOP	S	***	FIGLINE001 (from standard catalog)	x#
EXP-MT	T	Exposure to concomitant macitentan and tadalafil up to EOMOP	S		EXP0001	x#
EXP-MT	F	Exposure to concomitant macitentan and tadalafil up to EOMOP	S		FIGLINE001 (from standard catalog)	x#
EXP-MTS	T	Exposure to concomitant macitentan and tadalafil and selexipag/placebo up to EOMOP	S		EXP0001	x#
EXP-MTS	F	Exposure to concomitant macitentan and tadalafil and selexipag/placebo up to EOMOP	S		FIGLINE001 (from standard catalog)	x#

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
DOS-S	T	Maximum and weighted-average double-blind treatment daily dose up to EOMOP	S	***	EXP004	x#
DOS-TM	T	Individual maintenance dose and maximum tolerated dose of double-blind study treatment up to EOMOP	S	x***	EXP005	x#
DOS	L	Study medication dosing records	S		LSTDOS001	x

*T = Summary table, L = Listing, F=Figure, **S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions, # without 'up to EOMOP' in the title

13.4.2 Study treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
PWDT	T	Reasons for premature discontinuation of study treatment up to EOMOP	S	x***	DISP003	x#
PWDT	L	Listing of reasons for premature discontinuation of study and study treatment	S		LSTDSP001	x

*T = Summary table, L = Listing, ** S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions, # without 'up to EOMOP' in the title

13.5 Study withdrawal

See Section 13.1.

13.6 Primary efficacy analyses

13.6.1 Main analysis

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
MAIN	T	Analysis of covariance: PVR ratio of Week 26 to baseline	FAS	x	MAIN001

*T = Summary table, **FAS = Full analysis set

13.6.2 Supportive/sensitivity analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
MAIN	T	Analysis of covariance: PVR ratio of Week 26 to baseline	mFAS[1], P		MAIN001
MAIN-COMP	T	Analysis of covariance: PVR ratio of Week 26 to baseline in subjects who took all three study medications until Week 26	mFAS		MAIN001
PVR-SUM	T	Summary and change from baseline to Week 26 of PVR	FAS	x***	SUM001
MAIN-IMP2	T	Analysis of covariance: PVR ratio of Week 26 to baseline (alternative imputation)	FAS	x	MAIN001
MAIN-NOADJ	T	Analysis of covariance: PVR ratio of Week 26 to baseline (without adjustment)	FAS	x	MAIN001
MAIN-NOLOG	T	Analysis of covariance: Change from Baseline to Week 26 in PVR (no log-transformation)	FAS	x	MAIN001
MAIN-NOIMP	T	Analysis of covariance: PVR ratio of Week 26 to baseline (observed cases)	FAS	x	MAIN001
MAIN-MI	T	Multiple imputation analysis of the primary endpoint	FAS	x	MI001

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
MAIN-IMP3	T	Analysis of covariance: PVR ratio of Week 26 to baseline (alternative imputation 2)	FAS	x	MAIN001
MAIN	F	Scatter plot of change from baseline in PVR (Recalculated and LOCF) at Week 26 versus baseline	FAS		FIGSCAT001 (from standard catalog)

*T = Summary table, F = Figure, ** FAS = Full analysis set, mFAS = Modified full analysis set, P = Per-protocol analysis set, [1] only if mFAS is ≥ 5% different from FAS, ***Created on blinded combined groups for IDMC open sessions

13.6.3 Subgroup analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
PVR-SUB	T	Summary and change from baseline to Week 26 of PVR by subgroups *[region, WHO FC, age, gender, PAH etiology], one page per subgroup, show visits baseline and Week 26*	FAS		SUM001	
MAIN-SUB	T	Analysis of covariance: PVR ratio of Week 26 to baseline by subgroups *[region, WHO FC, age, gender, race, PAH etiology], one page per subgroup*	FAS		MAIN001	
MAIN-SUB	F	Forest plot of Analysis of covariance: PVR ratio of Week 26 to baseline by subgroups *[region, WHO FC, age, gender, race, PAH etiology]*	FAS	x	FIGFOREST001	
PVR-COMP	T	Summary and change from baseline to Week 26 of PVR in subjects who took all three study medications until Week 26	mFAS		SUM001	
RHC	L	Listing of right-heart catheterization results	SCR		LSTRHC001	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, P = Per-protocol analysis set, S = Safety analysis set

13.6.4 Secondary efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
MWD-MAIN	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance	FAS, mFAS[1], P	x (FAS)	MAIN001	
MWD	F	Scatter plot of change from baseline in six-minute walk distance at Week 26 versus baseline	FAS		FIGSCAT001 (from standard catalog)	
MWD-COMP	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance in subjects who took all three study medications until Week 26	mFAS		MAIN001	
MWD-MAIN-IMP2	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance (alternative imputation)	FAS	x	MAIN001	
MWD-MAIN-NOADJ	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance (without adjustment)	FAS	x	MAIN001	
MWD-MI	T	Multiple imputation analysis of 6MWD	FAS	x	MI001	
MWD-MAIN-NOIMP	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance (observed cases)	FAS	x	MAIN001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
MWD-MM	T	Repeated measures model: Change from baseline in six-minute walk distance to Week 26	FAS	x	MMRM001	
MWD-MAIN-IMP3	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance (alternative imputation 2)	FAS	x	MAIN001	
MWD-SUB	T	Summary and change from baseline of six-minute walk distance by visit and subgroups *[region, WHO FC, age, gender, PAH etiology], one page per subgroup]*	FAS		SUM001	
MWD-MAIN-SUB	T	Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance by subgroups *[region, WHO FC, age, gender, PAH etiology], one page per subgroup*	FAS		MAIN001	
MWD-MAIN-SUB	F	Forest plot of Analysis of covariance: Change from baseline to Week 26 in six-minute walk distance by subgroups *[region, WHO FC, age, gender, race, PAH etiology]*	FAS	x	FIGFOREST001	
MWD-SUMC	T	Summary and change from baseline of six-minute walk distance by visit in subjects who took all three study medications until Week 26	mFAS		SUM001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
MWD	L	Listing of six-minute walk test results	SCR		LSTMWD001	x
BNP-MAIN	T	Analysis of covariance: NT-proBNP ratio of Week 26 to baseline	FAS, mFAS[1], P	x (FAS)	MAIN001	
BNP-COMP	T	Analysis of covariance: NT-proBNP ratio of Week 26 to baseline in subjects who took all three study medications until Week 26	mFAS		MAIN001	
BNP-MM	T	Repeated measures model: Ratio to baseline in NT-proBNP up to Week 26	FAS		MMRM001	
BNP-MAIN-IMP2	T	Analysis of covariance: NT-proBNP ratio of Week 26 to baseline (alternative imputation)	FAS		MAIN001	
BNP-MAIN-NOIMP	T	Analysis of covariance: NT-proBNP ratio of Week 26 to baseline (observed cases)	FAS		MAIN001	
BNP-SUMC	T	Summary and change from baseline of NT-proBNP by visit in subjects who took all three study medications until Week 26	mFAS		SUM001	
BNP	L	Listing of NT-proBNP	SCR		LSTLB001	x
ABW	T	Logistic regression: Absence of worsening from baseline to Week 26 in WHO functional class	FAS, mFAS[1], P	x (FAS[***])	BIN001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
ABW-IMP2	T	Logistic regression: Absence of worsening from baseline to Week 26 in WHO functional class (alternative imputation)	FAS		BIN001	
ABW-NOIMP	T	Logistic regression: Absence of worsening from baseline to Week 26 in WHO functional class (observed cases)	FAS		BIN001	
ABW-COMP	T	Logistic regression: Absence of worsening from baseline to Week 26 in WHO functional class in subjects who took all three study medications until Week 26	mFAS		BIN001	
WHO-SHF	T	Shift table of WHO functional class from baseline to Week 26	FAS	x	BIN004	
WHO	L	Listing of WHO functional class	SCR		LSTWHO001	x
RHC-MAIN	T	Analysis of covariance: Change from baseline to Week 26 in hemodynamic parameters other than PVR *[Summarize mPAP, CI, TPR, mRAP, Venous oxygen saturation]*	FAS, mFAS[1], P	x (FAS)	MAIN001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
RHC-COMP	T	Analysis of covariance: Change from baseline to Week 26 in hemodynamic parameters other than PVR in subjects who took all three study medications until Week 26 *[Summarize mPAP, CI, TPR, mRAP, Venous oxygen saturation]*	mFAS		MAIN001	
RHC-NOIMP	T	Analysis of covariance: Change from baseline to Week 26 in hemodynamic parameters other than PVR (observed cases) *[Summarize mPAP, CI, TPR, mRAP, Venous oxygen saturation]*	FAS		MAIN001	
RHC-SUM	T	Summary and change from baseline of hemodynamic parameters other than PVR	FAS, mFAS[1], P	***	SUM001	
RHC-SUMC	T	Summary and change from baseline of hemodynamic parameters other than PVR in subjects who took all three study medications until Week 26	mFAS		SUM001	
TTP	T	Time to first disease progression event (up to EOMOP + 7 days)	FAS, mFAS[1], P	x (FAS***)	TTE001	
TTP	F	Time to first disease progression event (up to EOMOP + 7 days)	FAS, mFAS[1], P	x (FAS***)	FIGLINE002 (from standard catalog)	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
PROG	T	Reason for disease progression (up to EOMOP + 7 days)	FAS, mFAS[1], P	x (FAS[***])	TTE002	
PROG	L	Listing of disease progression events as adjudicated by the clinical events committee	SCR		LSTPROG001	x
TTP-COMP	T	Time to first disease progression event (up to EOMOP + 7 days) in subjects who took all three study medications until Week 26	mFAS		TTE001	
TTP-COMP	F	Time to first disease progression event (up to EOMOP + 7 days) in subjects who took all three study medications until Week 26	mFAS		FIGLINE002 (from standard catalog)	
PROG-COMP	T	Reason for disease progression (up to EOMOP + 7 days) in subjects who took all three study medications until Week 26	mFAS		TTE002	
TTP-XC	T	Time to first disease progression event (up to at EOMOP + 7 days or day of last drug intake of any of the three study medications + 7 days, whichever is the earliest)	FAS		TTE001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TTP-XC	F	Time to first disease progression event (up to at EOMOP + 7 days or day of last drug intake of any of the three study medications + 7 days, whichever is the earliest)	FAS		FIGLINE002 (from standard catalog)	
PROG-XC	T	Reason for disease progression (up to at EOMOP + 7 days or day of last drug intake of any of the three study medications + 7 days, whichever is the earliest)	FAS		TTE002	
TTP-XC2	T	Time to first disease progression event (up to EOMOP + 7 days or end of double-blind study treatment + 7 days, whichever is the earliest) in patients in FAS who received at least one dose of double-blind study treatment	FAS		TTE001	
TTP-XC2	F	Time to first disease progression event (up to EOMOP + 7 days or end of double-blind study treatment + 7 days, whichever is the earliest) in patients in FAS who received at least one dose of double-blind study treatment	FAS		FIGLINE002 (from standard catalog)	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
PROG-XC2	T	Reason for disease progression (up to EOMOP + 7 days or end of double-blind study treatment + 7 days, whichever is the earliest) in patients in FAS who received at least one dose of double-blind study treatment	FAS		TTE002	
TTP-XC3	T	Time to first disease progression event (up to EOS)	FAS		TTE001	Only after EOS
TTP-XC3	F	Time to first disease progression event (up to EOS)	FAS		FIGLINE002 (from standard catalog)	Only after EOS
PROG-XC3	T	Reason for disease progression (up to EOS)	FAS		TTE002	Only after EOS

*T = Summary table, L = Listing, F = Figure, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set, P = Per-protocol analysis set, [1] only if mFAS is ≥5% different from FAS, ***Created on blinded combined groups for IDMC open sessions

13.7 Other efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
MWD-SUM	T	Summary and change from baseline of six-minute walk distance by visit up to EOMOP	FAS	***	SUM001	
BNP-SUM	T	Summary and change from baseline of NT-proBNP by visit up to EOMOP	FAS	(FAS***)	SUM001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
ABW-SUM	T	Summary of absence of worsening from baseline to all visits in WHO functional class up to EOMOP	FAS	***	BIN002	
UNS-SUM	T	Summary of unsatisfactory clinical response up to EOMOP	FAS	***	BIN003	
UNS	L	Listing of unsatisfactory response criteria	SCR		LSTUNS001	x
GOL-SUM	T	Number of treatment goals met at Week 26	FAS	***	SUM002	
GOLS	T	Treatment goals shift table from baseline to Week 26	FAS		BIN005	
GOL	L	Listing of treatment goals met	SCR		LSTGOL001	x
IMP	T	Logistic regression: Improvement from baseline to Week 26 in WHO functional class	FAS		BIN005	
TTP_FHO	T	Time to first hospitalization (all causes) up to EOMOP	FAS		TTE001	
TTP_FHO	F	Time to first hospitalization (all causes) up to EOMOP	FAS		FIGLINE002 (from standard catalog)	
TTP_FHOPAH	T	Time to first hospitalization for worsening PAH up to EOMOP	FAS		TTE001	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TTP_FHOPAH	F	Time to first hospitalization for worsening PAH up to EOMOP	FAS		FIGLINE002 (from standard catalog)	
HO_POI	T	Annualized rate of hospitalizations (all causes) up to EOMOP	FAS		HOSP001	
HOPAH_POI	T	Annualized rate of hospitalizations for worsening PAH up to EOMOP	FAS		HOSP001	
HO_DUR	T	Annualized rate of days spent in hospital (all causes) up to EOMOP	FAS		HOSP002	
HOPAH_DUR	T	Annualized rate of days spent in hospital for worsening PAH up to EOMOP	FAS		HOSP002	
SAE_HOS	L	Listing of serious adverse events leading to hospitalization	SCR		LSTHOS001	x

*T = Summary table, L = Listing, F=Figure, **SCR = Screened analysis set, FAS = Full analysis set, ***Created on blinded combined groups for IDMC open sessions

13.8 Safety analyses

13.8.1 Adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TEAE-SOC	T	Incidence of treatment-emergent adverse events up to EOMOP by primary system organ class and preferred term	S	x***	LAYAE001 (from standard catalog)	x#
TEAE-PT	T	Incidence of treatment-emergent adverse events up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	x#
TEAE-SOC-M	T	Incidence of treatment-emergent adverse events related to macitentan up to EOMOP by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	x#
TEAE-PT-M	T	Incidence of treatment-emergent adverse events related to macitentan up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	x#
TEAE-SOC-T	T	Incidence of treatment-emergent adverse events related to tadalafil up to EOMOP by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	x#
TEAE-PT-T	T	Incidence of treatment-emergent adverse events related to tadalafil up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	x#
TEAE-SOC-S	T	Incidence of treatment-emergent adverse events related to selexipag/placebo up to EOMOP by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	x#

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TEAE-PT-S	T	Incidence of treatment-emergent adverse events related to selexipag/placebo up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	x#
TEAE-INT-PT	T	Incidence of treatment-emergent adverse events up to EOMOP by maximum intensity and preferred term	S	***	LAYAE003 (from standard catalog)	
TEAE-FREQ	T	Incidence of the most frequent (at least 5% in any treatment group) treatment-emergent adverse events up to EOMOP, by preferred term	S	x***	LAYAE002 (from standard catalog)	
SCR-AE-SOC	T	Incidence of AEs from informed consent signature till initiation of first study drug −1 day by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
SCR-AE-PT	T	Incidence of AEs from informed consent signature till initiation of first study drug −1 day by preferred term	S	***	LAYAE002 (from standard catalog)	
AE-1EOMOP-SOC	T	Incidence of adverse events with onset between Day 1 and end of main observation period, by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)	
AE-1EOMOP-PT	T	Incidence of adverse events with onset between Day 1 and end of main observation period, by preferred term	S		LAYAE002 (from standard catalog)	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
AE-1DB-SOC	T	Incidence of adverse events with onset between Day 1 and start of double-blind treatment, by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
AE-1DB-PT	T	Incidence of adverse events with onset between Day 1 and start of double-blind treatment, by preferred term	S	***	LAYAE002 (from standard catalog)	
AE-M-SOC	T	Incidence of adverse events with onset between Day 1 and 30 days after macitentan treatment or EOMOP, whichever is earlier, by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
AE-M-PT	T	Incidence of adverse events with onset between Day 1 and 30 days after macitentan treatment or EOMOP, whichever is earlier, by preferred term	S	***	LAYAE002 (from standard catalog)	
AE-T-SOC	T	Incidence of adverse events with onset between Day 1 and 30 days after tadalafil treatment or EOMOP, whichever is earlier, by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
AE-T-PT	T	Incidence of adverse events with onset between Day 1 and 30 days after tadalafil treatment or EOMOP, whichever is earlier, by preferred term	S	***	LAYAE002 (from standard catalog)	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
AE-S-SOC	T	Incidence of adverse events with onset between Day 1 and 30 days after selexipag/placebo treatment or EOMOP, whichever is earlier, by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
AE-S-PT	T	Incidence of adverse events with onset between Day 1 and 30 days after selexipag/placebo treatment or EOMOP, whichever is earlier, by preferred term	S	***	LAYAE002 (from standard catalog)	
AE-EOMEOT-SOC	T	Incidence of adverse events with onset between EOMOP and 30 days after EOT by primary system organ class and preferred term in patients with ongoing treatment at EOMOP visit	S		LAYAE001 (from standard catalog)	Only after EOS
AE-EOMEOT-PT	T	Incidence of adverse events with onset between EOMOP and 30 days after EOT by preferred term in patients with ongoing treatment at EOMOP visit	S		LAYAE002 (from standard catalog)	Only after EOS
AE-EOTEOS-SOC	T	Incidence of adverse events with onset during follow up after EOT by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	Only after EOS
AE-EOTEOS-PT	T	Incidence of adverse events with onset during follow up after EOT by preferred term	S	***	LAYAE002 (from standard catalog)	Only after EOS
AE-S-PERI-PT	T	Incidence of adverse events with onset during selexipag/placebo titration and maintenance periods up to EOMOP by preferred term	S		AETM002	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
AE-S-PERI-SOC	T	Incidence of adverse events with onset during selexipag/placebo titration and maintenance periods up to EOMOP by primary system organ class and preferred term	S		AETM001	
TEAE2-S-SOC	T	Incidence of adverse events with onset between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment or EOMOP, whichever is earlier, by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)	
TEAE2-S-PT	T	Incidence of adverse events with onset between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment or EOMOP, whichever is earlier, by preferred term	S		LAYAE002 (from standard catalog)	
AE	L	Listing of adverse events	SCR		LSTAE001	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions, # without 'up to EOMOP' in the title

13.9 Deaths and serious adverse events

13.9.1 Deaths

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
DTH-SOC	T	Study deaths up to EOMOP by primary system organ class and preferred term	S	x***	LAYAE001 (from standard catalog)	x#

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
DTH	L	Listing of study deaths	SCR	***	LSTCSR072 (from standard catalog)	x
AEDTH	L	Listing of all adverse events leading to death	SCR		LSTAE001	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions, # without 'up to EOMOP' in the title

13.9.2 Serious adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TESAE-SOC	T	Incidence of treatment-emergent serious adverse events up to EOMOP by primary system organ class and preferred term	S	x***	LAYAE001 (from standard catalog)	x#
TESAE-PT	T	Incidence of treatment-emergent serious adverse events up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	x#
TESAE-SOC-M	T	Incidence of treatment-emergent serious adverse events related to macitentan up to EOMOP by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
TESAE-PT-M	T	Incidence of treatment-emergent serious adverse events related to macitentan up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TESAE-SOC-T	T	Incidence of treatment-emergent serious adverse events related to tadalafil up to EOMOP by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
TESAE-PT-T	T	Incidence of treatment-emergent serious adverse events related to tadalafil up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	
TESAE-SOC-S	T	Incidence of treatment-emergent serious adverse events related to selexipag/placebo up to EOMOP by primary system organ class and preferred term	S	***	LAYAE001 (from standard catalog)	
TESAE-PT-S	T	Incidence of treatment-emergent serious adverse events related to selexipag/placebo up to EOMOP by preferred term	S	***	LAYAE002 (from standard catalog)	
TESAE-SOC-DB	T	Incidence of treatment-emergent serious adverse events up to EOMOP by primary system organ class and preferred term in patients who received at least one dose of double-blind study medication	S	***	LAYAE001 (from standard catalog)	
TESAE-PT-DB	T	Incidence of treatment-emergent serious adverse events up to EOMOP by preferred term in patients who received at least one dose of double-blind study medication	S	***	LAYAE002 (from standard catalog)	
SAE-ALL	L	Listing of serious adverse events	SCR	***	LSTAE001	x

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
SAE-PRI	L	Listing of serious adverse events occurring prior to first intake of study medication	SCR	***	LSTAE001	
SAE-POST	L	Listing of serious adverse events occurring more than 30 days after last dose of study medication	SCR	***	LSTAE001	x
SAEPAH	L	Listing of serious adverse events occurring after the start of a new PAH therapy	SCR		LSTAE001	x

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions, # without 'up to EOMOP' in the title

13.9.3 Adverse events leading to treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TEAE-DC-SOC-M	T	Incidence of treatment-emergent adverse events leading to discontinuation of macitentan up to EOMOP, by primary system organ class and preferred term	S	x***	LAYAE001 (from standard catalog)	x#
TEAE-DC-PT-M	T	Incidence of treatment-emergent adverse events leading to discontinuation of macitentan up to EOMOP, by preferred term	S	***	LAYAE002 (from standard catalog)	x#
TEAE-DC-SOC-T	T	Incidence of treatment-emergent adverse events leading to discontinuation of tadalafil up to EOMOP, by primary system organ class and preferred term	S	x***	LAYAE001 (from standard catalog)	x#
TEAE-DC-PT-T	T	Incidence of treatment-emergent adverse events leading to discontinuation of tadalafil up to EOMOP, by preferred term	S	***	LAYAE002 (from standard catalog)	x#

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout	Rerun after EOS
TEAE-DC-SOC-S	T	Incidence of treatment-emergent adverse events leading to discontinuation of selexipag/placebo up to EOMOP, by primary system organ class and preferred term	S	x***	LAYAE001 (from standard catalog)	x#
TEAE-DC-PT-S	T	Incidence of treatment-emergent adverse events leading to discontinuation of selexipag/placebo up to EOMOP, by preferred term	S	***	LAYAE002 (from standard catalog)	x#

*T = Summary table, ** S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions,
without 'up to EOMOP' in the title

13.9.4 Other significant adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
SEL-TEAE-RSK	T	Incidence of selexipag treatment-emergent adverse events up to EOMOP by important identified or potential risk and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo + 30 days will be shown]*.	S	x***	AERSK001
TEAE-HYPO-RSK	T	Incidence of treatment-emergent symptomatic hypotension adverse events up to EOMOP, by preferred term	S	x***	LAYAE002 (from standard catalog)
SEL-AE-SOC	T	Incidence of adverse events during selexipag/placebo exposure up to EOMOP, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
SEL-AE-PT	T	Incidence of adverse events during selexipag/placebo exposure up to EOMOP, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE002 (from standard catalog)
SEL-SAE-SOC	T	Incidence of serious adverse events during selexipag/placebo exposure up to EOMOP, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE001 (from standard catalog)
SEL-SAE-PT	T	Incidence of serious adverse events during selexipag/placebo exposure up to EOMOP, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE002 (from standard catalog)
SEL-AE-R-SOC	T	Incidence of adverse events during selexipag/placebo exposure up to EOMOP, related to selexipag/placebo, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE001 (from standard catalog)
SEL-AE-R-PT	T	Incidence of adverse events during selexipag/placebo exposure up to EOMOP, related to selexipag/placebo, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE002 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
SEL-AE-DC-SOC	T	Incidence of adverse events during selexipag/placebo exposure leading to discontinuation of selexipag/placebo up to EOMOP, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE001 (from standard catalog)
SEL-AE-DC-PT	T	Incidence of adverse events during selexipag/placebo exposure leading to discontinuation of selexipag/placebo up to EOMOP, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE002 (from standard catalog)
SEL-AE-DTH-SOC	T	Incidence of adverse events during selexipag/placebo exposure leading to death up to EOMOP, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	***	LAYAE001 (from standard catalog)
TEAE-SOC-SUB	T	Incidence of treatment-emergent adverse events up to EOMOP by primary system organ class, preferred term, age, group gender and race	S		LAYAE001 (from standard catalog)
TEAE2-S-PROST-SOC	T	Incidence of adverse events typical of prostanoid treatments with onset between start date of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment or EOMOP whichever is earlier.	S		LAYAE001 (from standard catalog)

*T = Summary table, **S=Safety analysis set, ***Created on blinded combined groups for IDMC open sessions

13.10 Summaries of adverse events for disclosure (EudraCT and ClinicalTrials.gov)

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
TESAE-DTH-SOC	T	Incidence of treatment-emergent serious adverse events with fatal outcome up to EOMOP by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)
TESAE-DTH-SOC-T	T	Incidence of treatment-emergent serious adverse events with fatal outcome related to tadalafil up to EOMOP by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)
TESAE-DTH-SOC-M	T	Incidence of treatment-emergent serious adverse events with fatal outcome related to macitentan up to EOMOP by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)
TESAE-DTH-SOC-S	T	Incidence of treatment-emergent serious adverse events with fatal outcome related to selexipag/placebo up to EOMOP by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)
TENSAE-5PCT-COS	T	Incidence of treatment-emergent non-serious adverse events with an incidence of 5% or higher in any treatment group up to EOMOP by primary system organ class and preferred term	S		LAYAE001 (from standard catalog)

*T = Summary table, **S = Safety analysis set

13.11 Laboratory tests

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
LB-SUM	T	Summary and change from baseline of quantitative laboratory values up to EOMOP	S	***	SUM001
LB-ABN	T	Incidence of treatment-emergent marked laboratory values up to EOMOP	S	x***	LAB001
LB-ABN-SPEC	T	Incidence of treatment-emergent treatment notable laboratory values for hepatic safety up to EOMOP	S	x***	LAB002
LB-DISH	F	Scatter plot of maximum ALT versus concomitant bilirubin (eDISH plot) up to EOMOP	S	***	FIGSCAT001 (from standard catalog)
LB-ABN	L	Listing of all parameters with marked laboratory values *[List all values of the laboratory parameter where a marked abnormal value occurred]*	SCR	***	LSTLB001
LB	L	Listing of all laboratory values	SCR		LSTLB001
PREG	L	Listing of pregnancy test results *[Do not display columns for reference range and changes from baseline]*	SCR		LSTLB001

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions

13.12 Vital signs and body weight

Output name	Display*	Title (Description)	Analysis set(s)**	Key output	Mock layout
VS-SUM	T	Summary and change from baseline of vital signs up to EOMOP	S	***	SUM001
VS-ABN	T	Incidence of notable treatment-emergent blood pressure values up to EOMOP	S	***	VS001
VS-ABN	L	List of notable treatment-emergent blood pressure values *[List all values of the parameter where a marked abnormal value occurred]*	SCR		LSTCSR091 (from standard catalog)
VS	L	Listing of vital signs	SCR		LSTCSR091 (from standard catalog)

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set, ***Created on blinded combined groups for IDMC open sessions

14 REFERENCES

[D-18.392] Protocol AC-065A308 TRITON: The efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension: A multi-center, double-blind, placebo-controlled, Phase 3b study. Actelion Pharmaceuticals Ltd; clinical study protocol, 4 December 2018.

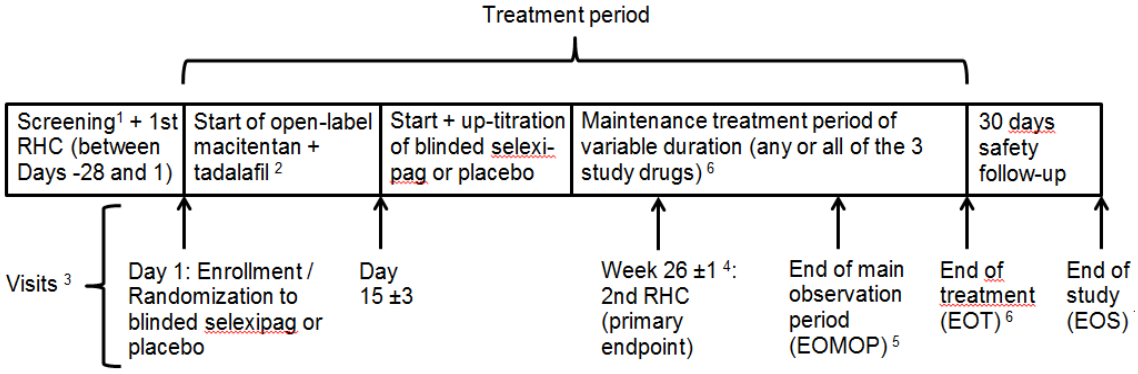
15 APPENDICES

Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS AC-065A308

TITLE	The efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension: A multi-center, double-blind, placebo-controlled, Phase 3b study
ACRONYM	TRITON
OBJECTIVES	Primary objective To compare the effect on pulmonary vascular resistance (PVR) of an initial triple oral regimen (macitentan, tadalafil, selexipag) versus an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with pulmonary arterial hypertension (PAH). Secondary objectives To compare an initial triple oral regimen (macitentan, tadalafil, selexipag) with an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH, with respect to cardio-pulmonary hemodynamics (other than PVR), exercise capacity, disease severity, disease progression events, safety, and tolerability. Exploratory objectives To compare an initial triple oral regimen (macitentan, tadalafil, selexipag) with an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH, with respect to additional disease severity endpoints.
DESIGN	This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel group, Phase 3b, efficacy and safety study comparing a triple oral regimen (macitentan, tadalafil, selexipag) with a dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH.

PERIODS



[1] Signed written informed consent is required prior to any study-mandated procedure (right heart catheterization [RHC] data obtained at the study site before informed consent signature but within 28 days prior to Day 1 are acceptable).

[2] Increase in tadalafil dose on Day 8 ± 3.

[3] For simplification, most visits between Day 1 and end of main observation period (EOMOP; as defined below) are not displayed. The complete visits and assessments are shown in Table 1.

[4] If double-blind treatment (selexipag/placebo) is discontinued before Week 26: The Week 26 assessments should be done either at Week 26 or before start of rescue therapy (prostacyclin, prostacyclin analog, or prostacyclin receptor agonist), whichever is first.

[5] The EOMOP is the data cutoff for the main efficacy and safety analyses, followed by data cleaning and unblinding of the treatment group allocation. The EOMOP visit is planned 26 ± 1 weeks after enrollment of the last subject. This timepoint will be announced by Actelion approximately 6 months in advance. The EOMOP visit is not required if within ± 2 weeks of a patient's Week 26 visit or Month 12, 18, 24, 30, etc. visit.

[6] All 3 study treatments are provided until the end of treatment (EOT) visit, which is planned approximately 4 months after the EOMOP visit. In order to allow sufficient time for the investigator to arrange any post-study therapy, Actelion will announce EOT approximately 10 months in advance, and unblind the treatment group allocation (selexipag or placebo) approximately 1 month prior to EOT. In case of premature discontinuation of all 3 study treatments, the EOT visit should be performed within 1 week but the subject should be followed up according to the schedule of assessments until end of study (EOS; as defined below).

[7] EOS is defined as the last data collection for a subject. The EOS visit for all subjects (regardless of whether they are receiving 3, 2, 1, or no study treatment) is planned approximately 5 months after the EOMOP visit. For all randomized patients, follow-up for disease progression (including death) will continue until EOS.

PLANNED DURATION	The study duration will be approximately 4 years, based on an assumed enrollment period of 3 years.
SITE(S) / COUNTRY(IES)	The study will be conducted at approximately 75 sites in approximately 20 countries.
SUBJECTS / GROUPS	Approximately 238 subjects will be randomized in a 1:1 ratio to the two treatment groups (approximately 119 subjects per group), stratified by region (North America versus rest of world) and WHO functional class (FC) at baseline (I/II versus III/IV).
INCLUSION CRITERIA	1. Signed informed consent prior to any study-mandated procedure. 2. Male or female ≥ 18 and ≤ 75 years of age at screening. 3. Initial PAH diagnosis < 6 months prior to Day 1. 4. RHC performed between Day −28 and Day 1 (RHC data obtained at the study site within this time frame, but before the study, i.e., before signed informed consent, are acceptable), meeting all the following criteria: • Mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. • Pulmonary artery wedge pressure or left ventricular end-diastolic pressure ≤ 15 mmHg. • PVR ≥ 480 dyn·sec/cm^5 (≥ 6 Wood Units). • Negative vasoreactivity test mandatory in idiopathic, heritable, and drug/toxin induced PAH (at this or a previous RHC). 5. Symptomatic PAH belonging to one of the following subgroups: • Idiopathic. • Heritable. • Drug or toxin induced. • Associated with one of the following: - Connective tissue disease. - HIV infection. - Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) ≥ 1 year after surgical repair. 6. 6-minute walk distance (6MWD) ≥ 50 m at screening. 7. Women of childbearing potential must: • Have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at the Day 1 visit, and • Agree to perform monthly pregnancy tests up to EOS, and • Agree to use reliable contraception from screening up to 1 month following discontinuation of the last study treatment.

	Reliable contraception must be started at least 11 days prior to Day 1.
EXCLUSION CRITERIA	1. Any PAH-specific drug therapy (e.g., any endothelin receptor antagonist [ERA], phosphodiesterase-5 inhibitor (PDE-5i), soluble guanylate cyclase stimulator, prostacyclin, prostacyclin analog, or prostacyclin receptor agonist) at any time prior to Day 1 (administration for vasoreactivity testing is permitted; previous PAH-specific drugs used intermittently for the treatment of digital ulcers or Raynaud's phenomenon are permitted if stopped > 6 months prior to Day 1). 2. Cardio-pulmonary rehabilitation program based on exercise (planned, or started ≤ 12 weeks prior to Day 1). 3. Body mass index (BMI) > 40 kg/m^2 at screening. 4. Presence of three or more of the following risk factors for heart failure with preserved ejection fraction at screening: • BMI > 30 kg/m^2. • Diabetes mellitus of any type. • Essential hypertension. • Coronary artery disease, i.e., any of the following: - History of stable angina or - More than 50% stenosis in a coronary artery (by coronary angiography) or - History of myocardial infarction or - History of or planned coronary artery bypass grafting and/or coronary artery stenting. 5. Acute myocardial infarction ≤ 12 weeks prior to screening. 6. Cerebrovascular events (e.g., transient ischemic attack, stroke) ≤ 12 weeks prior to screening. 7. Known permanent atrial fibrillation. 8. Systolic blood pressure < 90 mmHg at screening or Day 1. 9. Ongoing or planned treatment with organic nitrates and/or doxazosin. 10. Presence of one or more of the following signs of relevant lung disease at any time up to screening: • Diffusing capacity of the lung for carbon monoxide (DL_{CO}) < 40% of predicted UNLESS computed tomography reveals no or mild interstitial lung disease. • Forced vital capacity (FVC) < 60% of predicted. • Forced expiratory volume in one second (FEV_1) < 60% of predicted.

	Pulmonary function tests may be performed either with or without the use of bronchodilators, as per local clinical practice. 11. Known or suspected pulmonary veno-occlusive disease. 12. Documented severe hepatic impairment (with or without cirrhosis) according to National Cancer Institute organ dysfunction working group criteria, defined as total bilirubin > 3 × upper limit of the normal range (ULN) accompanied by aspartate aminotransferase (AST) > ULN (assessed at screening); and/or Child-Pugh Class C. 13. Serum AST and/or alanine aminotransferase (ALT) > 3 × ULN (assessed at screening). 14. Severe renal impairment (estimated creatinine clearance ≤ 30 mL/min/1.73 m^2) assessed at screening. 15. Ongoing or planned dialysis. 16. Hemoglobin < 100 g/L assessed at screening. 17. Known or suspected uncontrolled thyroid disease (hypo- or hyperthyroidism). 18. Loss of vision in one or both eyes because of non-arteritic ischemic optic neuropathy. 19. Treatment with strong inducers of cytochrome P450 3A4 (CYP3A4) (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort) ≤ 28 days prior to Day 1. 20. Treatment with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) and/or strong inhibitors of CYP2C8 (e.g., gemfibrozil) ≤ 28 days prior to Day 1. 21. Treatment with another investigational drug (planned, or taken ≤ 12 weeks prior to Day 1). 22. Hypersensitivity to any of the 3 study treatments or any excipient of their formulations (lactose, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, povidone, corn starch, sodium starch glycolate type A, polyvinyl alcohol, polysorbate 80, titanium dioxide, talc, xanthan gum, lecithin from soya, croscarmellose sodium, hypromellose, sodium laurylsulfate, triacetin, iron oxide yellow, iron oxide red, iron oxide black, d-mannitol, propylene glycol, carnauba wax). 23. Pregnancy, breastfeeding, or intention to become pregnant during the study. 24. Concomitant life-threatening disease with a life expectancy < 12 months. 25. Alcohol abuse.

	26. Any factor or condition likely to affect protocol compliance of the subject, as judged by the investigator.
STUDY TREATMENTS	**Investigational treatment** • Macitentan, open-label, oral tablet, 10 mg once daily (preferably always in the morning or always in the evening; to be recorded in the electronic Case Report Form [eCRF]). • Tadalafil, open-label, oral tablet, 20 mg one or two tablets once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF). • Selexipag oral tablet, 200 μg, one to eight tablets twice daily (in the morning and in the evening). A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. **Comparator treatment** • Macitentan, open-label, oral tablet, 10 mg once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF). • Tadalafil, open-label, oral tablet, 20 mg one or two tablets once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF). • Matching placebo to selexipag oral tablet, 200 μg, one to eight tablets twice daily (in the morning and in the evening). A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite.
CONCOMITANT THERAPY	Forbidden concomitant therapy: • Any PAH-specific drug (e.g., ERA, PDE-5i [also if used for erectile dysfunction], soluble guanylate cyclase stimulator, prostacyclin, prostacyclin analog, or prostacyclin receptor agonist) other than the 3 study treatments up to EOT, except if used as rescue therapy. If another PAH-specific drug is started (and the corresponding study treatment is stopped), subjects remain in the study, irrespective of whether they are receiving 3, 2, 1, or no study treatments. • Organic nitrates (other medications with vasodilatory effects must be used with caution). • Doxazosin.

	• Strong inducers of CYP3A4 (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort) during treatment with macitentan and/or tadalafil. • Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) during treatment with macitentan and/or tadalafil. • Strong inhibitors of CYP2C8 (e.g., gemfibrozil) during treatment with selexipag/placebo. • Any investigational drug other than the 3 study treatments. • Cardio-pulmonary rehabilitation programs based on exercise between Screening and the Week 26 visit.
ENDPOINTS	**Primary efficacy endpoint** The primary endpoint is the ratio of Week 26 to baseline PVR. **Secondary efficacy endpoints** 1. Change in 6MWD from baseline to Week 26. 2. Change in N-terminal pro B-type natriuretic peptide (NT-proBNP) from baseline to Week 26. 3. Absence of worsening in WHO FC from baseline to Week 26. 4. Change in RHC variables other than PVR (mPAP, cardiac index, total pulmonary resistance, mean right atrial pressure, venous oxygen saturation) from baseline to Week 26. 5. Time from randomization to the first disease progression event up to EOMOP + 7 days (adjudicated by the Clinical Events Committee [CEC]), defined as any of the following: a. Death (all causes; adjudicated for PAH relationship). b. Hospitalization for worsening PAH. c. Initiation of prostacyclin, a prostacyclin analog, or a prostacyclin receptor agonist for worsening PAH. d. Clinical worsening defined as a post-baseline decrease in 6MWD by > 15% from the highest 6MWD obtained at or after baseline, accompanied by WHO FC III or IV (both conditions confirmed at two consecutive post-baseline visits separated by 1–21 days). **Safety endpoints** • Treatment-emergent adverse events (AEs). • AEs leading to premature discontinuation of any of the 3 study treatments. • Treatment-emergent serious AEs.

	• Treatment-emergent deaths. • Treatment-emergent marked laboratory abnormalities. • Change from baseline in laboratory variables. • Change from baseline in vital signs.
ASSESSMENTS	See Table 1.
STATISTICAL METHOD-OLOGY	**Analysis sets:** The Safety Set includes all subjects who received at least one dose of any of the 3 study treatments. The Full Analysis Set (FAS) includes all randomized subjects. The Modified Full Analysis Set (Modified FAS) includes all subjects from the FAS who received at least one dose of each of the 3 study treatments. The Per-protocol Set includes all subjects from the FAS who received at least one dose of double-blind study treatment and who have no major protocol deviation. **Primary endpoint:** The primary efficacy endpoint is the ratio of Week 26 to baseline PVR. A geometric mean ratio (GMR) of Week 26 to baseline PVR < 1 corresponds to a reduction in PVR from baseline. **Statistical hypotheses:** The null hypothesis is that the GMR of Week 26 to baseline PVR is equal in the dual and triple therapy groups. The alternative hypothesis is that these GMRs are different, with a difference of –0.223 expressed on a log scale. **Type I and II errors and power:** The overall type I error (α) is set to 0.05 (two-sided). The type II error is set to 0.10 and therefore the power to 90%. **Primary analysis:** Following the intent-to-treat principle, the primary analysis will be conducted on the FAS. The ratio of Week 26 to baseline PVR will be log-transformed (base e) and analyzed using an analysis of covariance with factors for treatment group, region (as stratified at randomization), WHO FC (as stratified) and a continuous covariate for baseline log PVR. The treatment group difference (on log-scale) and its 95% confidence interval (CI) will be estimated based on the model.

	The triple versus dual ratio of GMRs and its 95% CI will be obtained by exponentiation. The null hypothesis will be rejected if the 95% CI around the ratio of the GMRs excludes 1. For subjects with a post-baseline PVR measurement obtained before Week 26, the (last) post-baseline PVR measurement will be carried forward. For subjects without a post-baseline PVR measurement, the baseline PVR will be carried forward (i.e., the ratio of Week 26 to baseline is set to one). Subjects with missing baseline PVR measurement will be excluded from analysis. **Secondary analyses:** To control for multiplicity across the primary and selected secondary efficacy endpoints, statistical analyses will be performed in the following sequence: change from baseline to Week 26 in 6MWD, change from baseline to Week 26 in NT-proBNP, time from randomization to first disease progression event, and absence of worsening from baseline to Week 26 in WHO FC. The changes from baseline to Week 26 in other RHC variables will be excluded from this hierarchical testing strategy as they include too many variables. Secondary efficacy variables will be analyzed for the FAS at $\alpha = 0.05$ (two-sided) using 95% CIs. **Safety analysis:** All safety analyses will be performed on the Safety Set using descriptive statistics. Additional safety analyses will be performed for the subset of subjects who received at least one dose of double-blind study treatment. **Interim analysis:** This study uses a group sequential design, and one interim analysis is planned when 33% of planned enrolled subjects in each arm have completed their Week 26 assessment or prematurely discontinued the study. This interim analysis is intended to test for futility (non-binding), in order to prevent continuing treating subjects with triple combination therapy if it is unlikely to show a clinical benefit for the subjects. However, as the interim analysis is designed to assess the efficacy of the triple versus the dual combination, it is not considering all safety aspects. Thus, an Independent Data Monitoring Committee (IDMC) will review efficacy, safety and tolerability data at regular intervals prior to and after the interim analysis.

	Sample size calculations: An integrated analysis of two bosentan studies (BENEFIT, AC-052-366, and EARLY, AC-052-364) and one macitentan study (the hemodynamic sub-study of SERAPHIN, AC-055-302) suggested that the within group standard deviation (SD) of the log-transformed ratio of Week 26 to baseline PVR is 0.41 (90% CI: 0.39–0.43). This is in line with published PVR data from studies of dual or triple combination therapy. For this trial, a more conservative SD = 0.5 on the log-scale was assumed. Four studies of initial dual therapy reported reductions (calculated) of PVR from baseline of 40% (n = 22; 95% CI: 27%–50%), 51% (n = 23; 95% CI: 42%–58%), 45% (n = 52; 95% CI: 38%–51%), and 54% (n=16; 95% CI: 48%–60%). One observational study of initial triple therapy reported a reduction (calculated) of PVR of 68% (n = 18; 95% CI: 62%–74%). Assuming 50% PVR reduction in the dual therapy group, 60% reduction in the triple therapy group (corresponding to a ratio of geometric means of 0.80, i.e., 20% difference in favor of triple therapy), and an overall type I error level of 5%, around 238 subjects would provide an overall 90% power at final analysis using a group sequential design and Pocock boundary, with interim analysis performed when 33% (i.e., 79 subjects) have completed the Week 26 PVR assessment.
STUDY COMMITTEES	• Steering Committee. • CEC. • IDMC. • Independent Liver Safety Data Review Board.

Appendix 2 Document history

Version	Effective Date	Reason
1.0	28-Jun-2016	Final Version 1.0
Amendment 1.0	8-Feb-2018	Included substantial changes in testing strategy and sample size from global protocol amendment 3; corrections of minor errors; clarifications for sample SAS code in Section 9; inclusion of estimand tables for primary and first secondary efficacy endpoint; addition of sensitivity analyses for primary and secondary efficacy endpoints.
Version 3.0 (Amendment 2)	20-Aug-2019	Some small changes are done following dry run 1. In addition, the following was added: - individual maximum tolerated dose definition - sensitivity analysis related to use of prostanoids PH therapy - additional definition of treatment goal (Galiè) - analysis of improvement in WHO FC - exploratory analyses of hospitalization. - additional summaries of adverse events

STATISTICAL ANALYSIS PLAN

FOR EOS CSR

THE EFFICACY AND SAFETY OF INITIAL TRIPLE VERSUS INITIAL DUAL ORAL COMBINATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED PULMONARY ARTERIAL HYPERTENSION: A MULTI-CENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3B STUDY (TRITON)

Purpose of Analysis	Clinical Study Report (analyses up to EOS) / final CSR
Investigational Drug	Selexipag / ACT-293987
Protocol Number	AC-065A308/TRITON
Actelion Document Number	D-20.063
Document Status/Version Number	Final
Date	26 February 2020

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Reviewer	PPD Clinical Trial Scientist
Reviewer	PPD, Senior Drug Safety Physician

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

ADaM	Analysis data model
CSR	Clinical study report
EOS	End-of-study
EOMOP	End of main observation period
EOT	End-of-treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
SAP	Statistical analysis plan

1 INTRODUCTION

The statistical analysis plan (SAP) for the clinical study report (CSR) of study AC-065A308 (TRITON) was finalized on 20 August 2019 (version 3) [D-19.253] prior to data unblinding, which occurred on 17 October 2019. Analyses performed following unblinding covered locked data up to the end of the main observation period (EOMOP) and are considered as the main analyses for efficacy and the interim analyses for safety. After the EOMOP, subjects remained on treatment up to their end-of-treatment (EOT) visit and remained in the study up to their end-of-study (EOS) visit. In the SAP [D-19.253] only specific analyses were planned to be performed after final database lock following EOS visit of all subjects. In the final CSR, safety will be fully described for the full treatment period, ie, including all data up to EOS. In addition, specific post hoc efficacy analyses performed up to EOMOP will be reproduced including all data up to EOS.

All definitions and analyses specifications are described in the main CSR SAP [D-19.253] and in the post hoc SAP for CSR [D-20.062].

Analyses described in this SAP are to be performed after the full database lock of the study. All data are converted into study data tabulation model datasets and are provided by data management. 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.

2 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

This section lists all outputs (ie, listings, tables and figures) produced to display the results of the analyses to be re-run with the full data package up to EOS.

The table, listing and figure naming conventions have 3 components: ***Type*** (T, L, F), ***Name*** (free text, not longer than ten characters), ***Suffix*** (for example, for analysis sets, or subgroups, not longer than four characters). Multiple suffixes can be added; components/suffixes are separated by '_'.

Mock layouts refer to specifications in the AC-065A308 'Layouts for TLFs' document.

2.1 Subject disposition

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
DISP	T	Subject disposition up to EOS	SCR	DISP001
PWDS	T	Reasons for premature discontinuation of study up to EOS	FAS	DISP004

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
VIS	L	Listing of study visits	SCR	LSTVIS001

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set.
EOS = end-of-study

2.2 Protocol deviations

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
PDALL	L	Listing of all protocol deviations	SCR	LSTPD001

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set

2.3 Subject characteristics

2.3.1 Previous and concomitant therapies

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
CM-SOC	T	Summary of therapies concomitant to study treatment up to EOS by Anatomical Therapeutic Chemistry (ATC) Class and Preferred Term	FAS, mFAS	LAYCMED001 (from standard catalog)
CM-PT	T	Summary of therapies concomitant to study treatment up to EOS by Preferred Term	FAS, mFAS	LAYCMED002
CM	L	Listing of subjects with previous and concomitant therapies	SCR	LSTCSR044 (with relative study day)

*T = Summary table, L = Listing, **SCR = Screened analysis set, FAS = Full analysis set, mFAS = Modified full analysis set
EOS = end-of-study

2.4 Study treatment exposure

2.4.1 Exposure

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
EXP-M	T	Exposure to macitentan up to EOS	S	EXP001

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
EXP-M	F	Exposure to macitentan up to EOS	S	FIGLINE001 (from standard catalog)
EXP-T	T	Exposure to tadalafil up to EOS	S	EXP001
EXP-T	F	Exposure to tadalafil up to EOS	S	FIGLINE001 (from standard catalog)
EXP-S	T	Exposure to double-blind study treatment (selexipag/placebo) up to EOS	S	EXP0001
EXP-S	F	Exposure to double-blind study treatment (selexipag/placebo) up to EOS	S	FIGLINE001 (from standard catalog)
EXP-MT	T	Exposure to concomitant macitentan and tadalafil up to EOS	S	EXP0001
EXP-MT	F	Exposure to concomitant macitentan and tadalafil up to EOS	S	FIGLINE001 (from standard catalog)
EXP-MTS	T	Exposure to concomitant macitentan and tadalafil and selexipag/placebo up to EOS	S	EXP0001
EXP-MTS	F	Exposure to concomitant macitentan and tadalafil and selexipag/placebo up to EOS	S	FIGLINE001 (from standard catalog)
DOS-S	T	Maximum and weighted-average double-blind treatment daily dose up to EOS	S	EXP004
DOS-TM	T	Individual maintenance dose and maximum tolerated dose of double-blind study treatment up to EOS	S	EXP005
DOS	L	Study medication dosing records	S	LSTDOS001

*T = Summary table, L = Listing, F=Figure, **S = Safety analysis set
EOS = end-of-study

2.4.2 Study treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
PWDT	T	Reasons for premature discontinuation of study treatment up to EOS	S	DISP003
PWDT	L	Listing of reasons for premature discontinuation of study and study treatment	S	LSTDSP001

*T = Summary table, L = Listing, ** S = Safety analysis set
EOS = end-of-study

2.5 Study withdrawal

See Section 2.1.

2.6 Primary efficacy analyses

2.6.1 Primary efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
RHC	L	Listing of right-heart catheterization results	SCR	LSTRHC001

*T = Summary table, L = Listing, **SCR = Screened analysis set

2.6.2 Secondary efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
MWD	L	Listing of six-minute walk test results	SCR	LSTMWD001
BNP	L	Listing of NT-proBNP	SCR	LSTLB001
WHO	L	Listing of WHO functional class	SCR	LSTWHO001
PROG	L	Listing of disease progression events as adjudicated by the clinical events committee	SCR	LSTPROG001

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TTP-XC3	T	Time to first disease progression event (up to EOS)	FAS	TTE001
TTP-XC3	F	Time to first disease progression event (up to EOS)	FAS	FIGLINE002 (from standard catalog)
PROG-XC3	T	Reason for disease progression (up to EOS)	FAS	TTE002

*T = Summary table, L = Listing, F = Figure, **SCR = Screened analysis set, FAS = Full analysis set
EOS = end-of-study; NT-proBNP = N-terminal pro B-type natriuretic peptide; WHO = World Health Organization

2.7 Other efficacy analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
SAE_HOS	L	Listing of serious adverse events leading to hospitalization	SCR	LSTHOS001
TTP-DTHEOS	F	Time to death up to EOS	FAS	FIGLINE002
TTP-DTHEOS	T	Time to death up to EOS	FAS	TTE001
RECEVENT-FREQEOS	T	Summary of (potentially) recurrent disease progression events up to EOS	FAS	RECEVENT01
RECEVENT-MODEOS	T	Negative binomial and Andersen-Gill models for (potentially) recurrent disease progression events up to EOS	FAS	RECEVENT02

*T = Summary table, L = Listing, F=Figure, **SCR = Screened analysis set, FAS= Full analysis set
EOS = end-of-study

2.8 Safety analyses

2.8.1 Adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE-SOC	T	Incidence of treatment-emergent adverse events up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE-PT	T	Incidence of treatment-emergent adverse events up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TEAE-SOC-M	T	Incidence of treatment-emergent adverse events related to macitentan up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TEAE-PT-M	T	Incidence of treatment-emergent adverse events related to macitentan up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TEAE-SOC-T	T	Incidence of treatment-emergent adverse events related to tadalafil up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TEAE-PT-T	T	Incidence of treatment-emergent adverse events related to tadalafil up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TEAE-SOC-S	T	Incidence of treatment-emergent adverse events related to selexipag/placebo up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TEAE-PT-S	T	Incidence of treatment-emergent adverse events related to selexipag/placebo up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TEAE-INT-PT	T	Incidence of treatment-emergent adverse events up to EOS by maximum intensity and preferred term	S	LAYAE003 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE-FREQ	T	Incidence of the most frequent (at least 5% in any treatment group) treatment-emergent adverse events up to EOS, by preferred term	S	LAYAE002 (from standard catalog)
AE-M-SOC	T	Incidence of adverse events with onset between Day 1 and 30 days after macitentan treatment or EOS, whichever is earlier, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
AE-M-PT	T	Incidence of adverse events with onset between Day 1 and 30 days after macitentan treatment or EOS, whichever is earlier, by preferred term	S	LAYAE002 (from standard catalog)
AE-T-SOC	T	Incidence of adverse events with onset between Day 1 and 30 days after tadalafil treatment or EOS, whichever is earlier, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
AE-T-PT	T	Incidence of adverse events with onset between Day 1 and 30 days after tadalafil treatment or EOS, whichever is earlier, by preferred term	S	LAYAE002 (from standard catalog)
AE-S-SOC	T	Incidence of adverse events with onset between Day 1 and 30 days after selexipag/placebo treatment or EOS, whichever is earlier, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
AE-S-PT	T	Incidence of adverse events with onset between Day 1 and 30 days after selexipag/placebo treatment or EOS, whichever is earlier, by preferred term	S	LAYAE002 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
AE-EOMEOT-SOC	T	Incidence of adverse events with onset between EOMOP and 30 days after last dose of study treatment by primary system organ class and preferred term in patients with ongoing treatment at EOMOP visit	S	LAYAE001 (from standard catalog)
AE-EOMEOT-PT	T	Incidence of adverse events with onset between EOMOP and 30 days after last dose of study treatment by preferred term in patients with ongoing treatment at EOMOP visit	S	LAYAE002 (from standard catalog)
AE-EOTEOS-SOC	T	Incidence of adverse events with onset during follow up after last dose of study treatment by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
AE-EOTEOS-PT	T	Incidence of adverse events with onset during follow up after last dose of study treatment by preferred term	S	LAYAE002 (from standard catalog)
AE-S-PERI-PT	T	Incidence of adverse events with onset during selexipag/placebo titration and maintenance periods up to EOS by preferred term	S	AETM002
AE-S-PERI-SOC	T	Incidence of adverse events with onset during selexipag/placebo titration and maintenance periods up to EOS by primary system organ class and preferred term	S	AETM001
TEAE2-S-SOC	T	Incidence of adverse events with onset between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment or EOS, whichever is earlier, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE2-S-PT	T	Incidence of adverse events with onset between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment or EOS, whichever is earlier, by preferred term	S	LAYAE002 (from standard catalog)
AE	L	Listing of adverse events	SCR	LSTAE001

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set
EOMOP = end of main observation period; EOS = end-of-study

2.9 Deaths and serious adverse events

2.9.1 Deaths

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
DTH-SOC	T	Study deaths up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
DTH	L	Listing of study deaths	SCR	LSTCSR072 (with relative study day and day off treatment)
AEDTH	L	Listing of all adverse events leading to death	SCR	LSTAE001

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set
EOS = end-of-study

2.9.2 Serious adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TESAE-SOC	T	Incidence of treatment-emergent serious adverse events up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TESAE-PT	T	Incidence of treatment-emergent serious adverse events up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TESAE-SOC-M	T	Incidence of treatment-emergent serious adverse events related to macitentan up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TESAE-PT-M	T	Incidence of treatment-emergent serious adverse events related to macitentan up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TESAE-SOC-T	T	Incidence of treatment-emergent serious adverse events related to tadalafil up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TESAE-PT-T	T	Incidence of treatment-emergent serious adverse events related to tadalafil up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TESAE-SOC-S	T	Incidence of treatment-emergent serious adverse events related to selexipag/placebo up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TESAE-PT-S	T	Incidence of treatment-emergent serious adverse events related to selexipag/placebo up to EOS by preferred term	S	LAYAE002 (from standard catalog)
TESAE-SOC-DB	T	Incidence of treatment-emergent serious adverse events up to EOS by primary system organ class and preferred term in patients who received at least one dose of double-blind study medication	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TESAE-PT-DB	T	Incidence of treatment-emergent serious adverse events up to EOS by preferred term in patients who received at least one dose of double-blind study medication	S	LAYAE002 (from standard catalog)
SAE-ALL	L	Listing of serious adverse events	SCR	LSTAE001
SAE-POST	L	Listing of serious adverse events occurring more than 30 days after last dose of study medication	SCR	LSTAE001
SAEPAH	L	Listing of serious adverse events occurring after the start of a new PAH therapy	SCR	LSTAE001

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set
EOS = end-of-study; PAH = pulmonary arterial hypertension

2.9.3 Adverse events leading to treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE-DC-SOC-M	T	Incidence of treatment-emergent adverse events leading to discontinuation of macitentan up to EOS, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TEAE-DC-PT-M	T	Incidence of treatment-emergent adverse events leading to discontinuation of macitentan up to EOS, by preferred term	S	LAYAE002 (from standard catalog)
TEAE-DC-SOC-T	T	Incidence of treatment-emergent adverse events leading to discontinuation of tadalafil up to EOS, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TEAE-DC-PT-T	T	Incidence of treatment-emergent adverse events leading to discontinuation of tadalafil up to EOS, by preferred term	S	LAYAE002 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE-DC-SOC-S	T	Incidence of treatment-emergent adverse events leading to discontinuation of selexipag/placebo up to EOS, by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TEAE-DC-PT-S	T	Incidence of treatment-emergent adverse events leading to discontinuation of selexipag/placebo up to EOS, by preferred term	S	LAYAE002 (from standard catalog)
	L	Listing of adverse events leading to discontinuation of any study treatment	SCR	LSTAE001

*T = Summary table, ** S = Safety analysis set
EOS = end-of-study

2.9.4 Other significant adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
SEL-TEAE-RSK	T	Incidence of selexipag treatment-emergent adverse events up to EOS by important identified or potential risk and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo + 30 days will be shown]*.	S	AERSK001
TEAE-HYPO-RSK	T	Incidence of treatment-emergent symptomatic hypotension adverse events up to EOS, by preferred term	S	LAYAE002 (from standard catalog)
SEL-AE-SOC	T	Incidence of adverse events during selexipag/placebo exposure up to EOS, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
SEL-AE-PT	T	Incidence of adverse events during selexipag/placebo exposure up to EOS, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE002 (from standard catalog)
SEL-SAE-SOC	T	Incidence of serious adverse events during selexipag/placebo exposure up to EOS, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE001 (from standard catalog)
SEL-SAE-PT	T	Incidence of serious adverse events during selexipag/placebo exposure up to EOS, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE002 (from standard catalog)
	T	Incidence of serious adverse events with onset between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment up to EOS, by preferred term	S	LAYAE002 (from standard catalog)
	T	Incidence of serious adverse events with onset between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment up to EOS, by primary system organ class and preferred term	S	LAYAE002 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
SEL-AE-R-SOC	T	Incidence of adverse events during selexipag/placebo exposure up to EOS, related to selexipag/placebo, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE001 (from standard catalog)
SEL-AE-R-PT	T	Incidence of adverse events during selexipag/placebo exposure up to EOS, related to selexipag/placebo, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE002 (from standard catalog)
SEL-AE-DC-SOC	T	Incidence of adverse events during selexipag/placebo exposure leading to discontinuation of selexipag/placebo up to EOS, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE001 (from standard catalog)
SEL-AE-DC-PT	T	Incidence of adverse events during selexipag/placebo exposure leading to discontinuation of selexipag/placebo up to EOS, by preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE002 (from standard catalog)
SEL-AE-DTH-SOC	T	Incidence of adverse events during selexipag/placebo exposure leading to death up to EOS, by primary system organ class and preferred term *[Only AEs with onset between first and last intake of selexipag/placebo will be shown]*.	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TEAE-SOC-SUB	T	Incidence of treatment-emergent adverse events up to EOS by primary system organ class, preferred term, age, group gender and race	S	LAYAE001 (from standard catalog)
TEAE2-S-PROST-SOC	T	Incidence of adverse events typical of prostanoid treatments with onset between start date of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment up to EOS.	S	LAYAE001 (from standard catalog)
	T	Incidence of adverse events typical of prostanoid treatments with onset during selexipag/placebo titration and maintenance periods between start date of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment up to EOS	S	AETM002

*T = Summary table, **S=Safety analysis set
AE = adverse event; EOS = end-of-study

2.10 Summaries of adverse events for disclosure (EudraCT and ClinicalTrials.gov)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TESAE-DTH-SOC	T	Incidence of treatment-emergent serious adverse events with fatal outcome up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TESAE-DTH-SOC-T	T	Incidence of treatment-emergent serious adverse events with fatal outcome related to tadalafil up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
TESAE-DTH-SOC-M	T	Incidence of treatment-emergent serious adverse events with fatal outcome related to macitentan up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TESAE-DTH-SOC-S	T	Incidence of treatment-emergent serious adverse events with fatal outcome related to selexipag/placebo up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)
TENSAE-5PCT-COS	T	Incidence of treatment-emergent non-serious adverse events with an incidence of 5% or higher in any treatment group up to EOS by primary system organ class and preferred term	S	LAYAE001 (from standard catalog)

*T = Summary table, **S = Safety analysis set
EOS = end-of-study

2.11 Laboratory tests

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
LB-SUM	T	Summary and change from baseline of quantitative laboratory values up to EOS	S	SUM001
LB-ABN	T	Incidence of treatment-emergent marked laboratory values up to EOS	S	LAB001
t-lb-abn-sel-s	T	Incidence of treatment-emergent marked laboratory values with onset date between start of selexipag/placebo treatment and 3 days after end of selexipag/placebo treatment up to EOS.	S	LAB001
LB-ABN-SPEC	T	Incidence of treatment-emergent treatment notable laboratory values for hepatic safety up to EOS	S	LAB002

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
LB-DISH	F	Scatter plot of maximum ALT versus concomitant bilirubin (eDISH plot) up to EOS	S	FIGSCAT001 (from standard catalog)
LB-ABN	L	Listing of all parameters with marked laboratory values *[List all values of the laboratory parameter where a marked abnormal value occurred]*	SCR	LSTLB001
LB	L	Listing of all laboratory values	SCR	LSTLB001
PREG	L	Listing of pregnancy test results *[Do not display columns for reference range and changes from baseline]*	SCR	LSTLB001

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set
ALT = alanine aminotransferase; EOS = end-of-study

2.12 Vital signs and body weight

Output name	Display*	Title (Description)	Analysis set(s)**	Mock layout
VS-SUM	T	Summary and change from baseline of vital signs up to EOS	S	SUM001
VS-ABN	T	Incidence of notable treatment-emergent blood pressure values up to EOS	S	VS001
VS-ABN	L	List of notable treatment-emergent blood pressure values *[List all values of the parameter where a marked abnormal value occurred]*	SCR	LSTCSR091 (from standard catalog)
VS	L	Listing of vital signs	SCR	LSTCSR091 (from standard catalog)

*T = Summary table, L = Listing, **SCR = Screened analysis set, S = Safety analysis set
EOS = end-of-study

3 REFERENCES

[D-19.253] Statistical analysis plan for clinical study report AC-065A308 TRITON: The efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension: A multi-center, double-blind, placebo-controlled, Phase 3b study. Actelion Pharmaceuticals Ltd; statistical analysis plan, 20 August 2019.

[D-20.062] Post-hoc Statistical analysis plan for interim clinical study report AC-065A308 TRITON: The efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed pulmonary arterial hypertension: A multi-center, double-blind, placebo-controlled, Phase 3b study. Actelion Pharmaceuticals Ltd; post-hoc statistical analysis plan, 21 February 2020.

4 APPENDICES

Appendix 1 Document history

Version	Effective Date	Reason
1.0	26-Feb-2020	Final Version 1.0