Selexipag / ACT-293987

Pulmonary Arterial Hypertension

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

Study Phase:	3b
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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Selexipag / ACT-293987

Indication

Pulmonary arterial hypertension

Protocol number, study acronym, study title

AC-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.

I approve the design of this study.

TITLE	NAME	DATE	SIGNATURE
Clinical Trial Physician	Maziar Assadi Gehr	4.12.2018	PPD
Clinical Trial Statistician	Nicolas Martin	4.12.2018	PPD

INVESTIGATOR SIGNATURE PAGE

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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.

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

I agree to conduct this study in accordance with the latest versions of the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Institutional Review Board or Independent Ethics Committee (IRB/IEC) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB/IEC and ensure approval by regulatory authorities (if applicable) have been obtained before the implementation of changes described in the amendment. I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to regulatory authorities worldwide.

	Country	Site number	Town	Date	Signature
Principal Investigator					

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BMI	Body mass index
BP	Blood pressure
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CL	Confidence limit
CO	Cardiac output
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CYP3A4	Cytochrome P450 3A4
DL_{CO}	Diffusing capacity of the lung for carbon monoxide
d/sSAP	Diastolic/systolic systemic arterial pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOMOP	End of main observation period
EOS	End of study
EOT	End of treatment
ERA	Endothelin receptor antagonist
FAS	Full Analysis Set
FC	Functional class

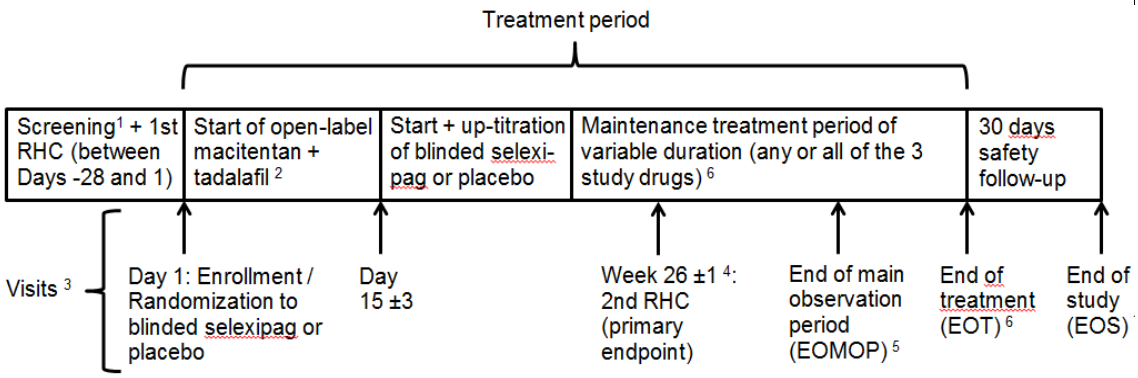
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LVEDP	Left ventricular end-diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
m/d/sPAP	Mean/diastolic/systolic pulmonary artery pressure
mRAP	Mean right atrial pressure
MTD	Maximum tolerated dose
NAION	Non-arteritic ischemic optic neuropathy
NT-proBNP	N-terminal pro B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PDE-5	Phosphodiesterase-5
PDE-5i	Phosphodiesterase-5 inhibitor
PH	Pulmonary hypertension
PI	Principal investigator
PPS	Per-protocol Set
PVOD	Pulmonary veno-occlusive disease

PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Steering Committee
SD	Standard deviation
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of the normal range
USPI	US package insert
VO_2	Volume of oxygen uptake
WHO	World Health Organization
WU	Wood Units

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.

Table 1 Visit and assessment schedule

PERIODS	Name	SCREE-NING	TREATMENT										FOLLOW-UP
	Duration	28 days											30 days
VISITS	Name	Scree-ning [6]	Random-ization							End of main observation period (EOMOP) [5,14]	End of Treatment (EOT) [5]	Unscheduled visits 1, 2, etc [3, 15]	End of Study (EOS) [1, 5]
	Time	Day −28 to Day 1	Day 1	Day 8 (± 3 days) [1]	Day 15 (± 3 days)	Weekly phone calls [2]	Week 12 (± 1 week)	Week 26 (± 1 week)	Month 12, 18, 24, 30, etc (± 2 weeks) [13]	Will be announced [11]	Will be announced [11]	Any time between Day 1 and EOS [3]	30–35 days after EOT [1,5]
Informed consent [10]		X											
Eligibility & demographics		X											
Medical history		X											
Right heart catheterization		X [10]						X				X	
Physical examination		X			X		X	X	X	X	X	X	
Vital signs (BP, HR)		X	X [7]		X		X	X	X	X	X	X	
WHO FC [15]		X	X [7]				X	X	X	X	X	X	
6MWD [15], Borg dysp. index		X	X [7]				X	X	X	X	X	X	
Laboratory tests general [17]		X [16]	X [7]				X	X	X	X	X	X	
Liver and hemoglobin tests [9]		X [16]	X [7]	Monthly [13] (± 1 week)							X	X	
Pregnancy test [8]		X	X	Monthly [13] (± 1 week)							X	X	X
Contraceptive methods docu		X [4]	X		X		X	X	X	X	X	X	X
Blood sampling biomarkers		X						X					
Study treatm. dispensing			X		X		X	X	X	X		X	
Study treatment return							X	X	X	X	X	X	
Previous/concom. therapies		X	X		X		X	X	X	X	X	X	
AEs, SAEs [12]		X	X	X	X	X	X	X	X	X	X	X	X

[1] Visit or phone call.

[2] Weekly phone calls during the up-titration phase of double-blind study treatment.

[3] Unscheduled visits may be performed at any time during the study and may include any of the indicated assessments, based on investigator judgment.

[4] Reliable contraception must be started at least 11 days prior to Day 1.

[5] EOMOP, EOT, EOS: See definitions under 'Periods' above.

[6] It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication). All screening assessments should then be repeated at the time of re-screening.

[7] Only needed if screening assessment > 7 days before Day 1.

[8] In women of childbearing potential only. Serum pregnancy tests at Screening, Week 12, Week 26, monthly (± 1 week) throughout the study, at EOMOP, EOT, and if pregnancy is suspected at any time during the study. Urine pregnancy tests at the Day 1 visit and if a monthly serum test is missed. At EOS either serum or urine pregnancy testing.

[9] Monthly (± 1 week) central laboratory testing of liver aminotransferases, total and direct bilirubin, and hemoglobin is mandatory throughout the study. For monthly testing, blood drawing is performed either at the study site, at a satellite laboratory close to where the subject lives, or by a phlebotomy service at the subject's home.

[10] Signed informed consent required before any study-mandated procedure. However, RHC data obtained at the study site within 28 days prior to Day 1 but before the study (i.e., before signed informed consent) are acceptable.

[11] Actelion will announce EOMOP approximately 6 months in advance and EOT approximately 10 months in advance. The treatment group allocation (unblinding) will be disclosed approximately 1 month prior to EOT.

[12] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after discontinuation of the last of the 3 study treatments must be reported.

[13] For this clinical trial, a month is defined as 30 days.

[14] 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.

[15] If any post-baseline decrease in 6MWD by > 15% from the highest 6MWD obtained at or after screening is observed, accompanied by WHO FC III or IV, then both the 6MWD and WHO FC must be reassessed at an unscheduled visit after 1–21 days.

[16] As an alternative to central laboratory tests, eligibility of subjects at Screening may be determined using local laboratory tests as long as the central laboratory kit is used in parallel. All local laboratory data including the normal ranges must be entered on dedicated eCRF pages.

[17] Laboratory tests general: Hematology, clinical chemistry including liver and hemoglobin tests, coagulation tests, and NT-proBNP.

6MWD = 6-minute walk distance; AE = adverse event; BP = blood pressure; eCRF = electronic case report form; EOMOP = end of main observation period; EOS = end of study; EOT = end of treatment; FC = functional class; HR = heart rate; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

PROTOCOL

1 BACKGROUND

1.1 Indication

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

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

The updated clinical classification of pulmonary hypertension (PH; Nice 2013) [Simonneau 2013] classifies the numerous conditions that are known to lead or be associated with the development of PAH into 4 groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause (idiopathic), in a familial setting (heritable), as the result of the use of certain drugs and toxins, or it can be associated with a connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.

1.2 Study treatments

Three PAH-specific drugs are used as study treatments in this trial: macitentan, tadalafil, and selexipag. Macitentan is an endothelin receptor antagonist (ERA) and acts via the endothelin pathway, tadalafil is a phosphodiesterase type 5 (PDE-5) inhibitor and acts via the nitric oxide pathway, and selexipag is an prostacyclin receptor agonist and acts via the prostacyclin pathway, i.e., when administered together, these drugs tackle all three key PAH therapeutical pathways mentioned in Section 1.1.

1.2.1 Macitentan

Macitentan is approved in the US, the European Union, and an increasing number of other countries for the treatment of PAH.

More detailed information on macitentan can be found in the Investigator's Brochure (IB) [Macitentan IB].

1.2.1.1 Nonclinical results

Macitentan is an orally active, non-peptide, potent dual endothelin receptor A and B antagonist. Macitentan showed dose dependent efficacy in nonclinical models of hypertension and PH. In nonclinical safety studies, no effects on normal physiological functions or ECG variables, including cardiac repolarization, were observed, with the exception of a decrease in arterial blood pressure (BP) observed in a cardiovascular study in dogs. Macitentan has no genotoxic and no carcinogenic potential. In the pivotal 26-week and 39-week toxicity studies, the exposures in animals at the no-observed-adverse-effect levels were above the anticipated clinical exposures and provided a margin of safety for studies in humans. Reproductive toxicity studies showed that macitentan is teratogenic without affecting male or female fertility. Teratogenicity is considered to be an ERA class effect.

1.2.1.2 Clinical pharmacology

During the Phase 1 program, more than 200 healthy subjects and about 30 subjects with renal and hepatic impairment were treated with macitentan. Macitentan was well tolerated in all studies. The most frequently reported adverse event (AE) was headache.

1.2.1.3 Clinical efficacy

Efficacy was established in a long-term study in PAH patients with predominantly WHO functional class (FC) II–III symptoms treated for an average of 2 years [Pulido 2013]. Patients had idiopathic or heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%), and were treated with macitentan monotherapy or in combination with PDE-5 inhibitors (PDE-5i) or inhaled prostanoids.

The trial demonstrated that macitentan 10 mg reduces the risk of morbidity/mortality in patients with symptomatic PAH, with a hazard ratio versus placebo of 0.55, 97.5% confidence limits (CLs): 0.32, 0.76, $p < 0.001$. This represents a risk reduction of 45% [Pulido 2013]. The effect of macitentan was observed regardless of whether the patient was receiving other therapy for PAH.

The placebo-corrected mean change in 6-minute walk distance (6MWD) from baseline to Month 6 showed an increase of 22.0 m (97.5% CLs: 3.2, 40.8) with macitentan 10 mg. The WHO FC improved from baseline to Month 6 in 13% of the patients in the placebo group, as compared with 22% of those in the group that received 10 mg of macitentan ($P = 0.006$) [Pulido 2013].

A hemodynamic sub-study showed a placebo-corrected mean reduction of PVR from baseline to Month 6 of 38.5% (97.5% CLs: 25.7, 49.0) with macitentan 10 mg [Pulido 2013].

1.2.1.4 Summary of safety profile

The safety of macitentan has been evaluated in a long-term placebo-controlled trial of 742 patients with symptomatic PAH [Pulido 2013, Macitentan IB]. The mean treatment duration was 103.9 weeks in the macitentan 10 mg group, and 85.3 weeks in the placebo group. The most commonly reported adverse drug reactions are nasopharyngitis (14.0%), headache (13.6%), and anaemia (13.2%). The majority of adverse reactions are mild to moderate in intensity. The overall incidence of treatment discontinuations because of adverse events was similar across macitentan 10 mg and placebo treatment groups (approximately 11%).

1.2.2 Tadalafil

Tadalafil is approved in the US [Adcirca USPI], the European Union [Adcirca SmPC], and many other countries (see local prescribing information) for the treatment of PAH.

1.2.2.1 Nonclinical results

Tadalafil is a selective inhibitor of PDE-5, the enzyme responsible for the degradation of cGMP. PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE-5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE-5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Nonclinical studies have shown that the effect of tadalafil is more potent on PDE-5 than on other phosphodiesterases.

For the nonclinical toxicology of tadalafil see the prescribing information [Adcirca SmPC, Adcirca USPI, local prescribing information].

1.2.2.2 Clinical pharmacology

In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Tadalafil must not be used in patients taking any form of organic nitrates.

For other pharmacodynamics effects, interactions, and the pharmacokinetics of tadalafil see the SmPC and USPI [Adcirca SmPC, Adcirca USPI, local prescribing information].

1.2.2.3 Clinical efficacy

Tadalafil was evaluated in a Phase 3, randomized, double-blind, 16-week placebo-controlled study conducted in 405 patients with PAH. Allowed background therapy included bosentan (maintenance dosing up to 125 mg twice daily). Subjects were randomly assigned to 1 of 5 treatment groups (tadalafil 2.5, 10, 20, 40 mg, or placebo) in

a 1:1:1:1:1 ratio. The mean age of all subjects was 54 years (range 14–90 years) with the majority of subjects being Caucasian (81%) and female (78%). PAH etiologies were predominantly idiopathic PAH (61%) and related to collagen vascular disease (24%). More than half (53%) of the subjects in the study were receiving concomitant bosentan therapy. The majority of subjects had a WHO FC III (65%) or II (32%). The mean baseline 6MWD was 343 meters. The primary efficacy endpoint was the change from baseline at Week 16 in 6MWD. In the tadalafil 40 mg treatment group, the placebo-adjusted mean increase in 6MWD was 33 meters (95% confidence interval [CI]: 15–50 meters; p = 0.0004). Placebo-adjusted changes in 6MWD at 16 weeks were evaluated in subgroups. In patients taking only tadalafil 40 mg (i.e., without concomitant bosentan), the placebo-adjusted mean change in 6MWD was 44 meters. In patients taking tadalafil 40 mg and concomitant bosentan therapy, the placebo adjusted mean change in 6MWD was 23 meters. There was less clinical worsening (defined as death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy [prostacyclin or prostacyclin analog, ERA, PDE-5i], or worsening WHO FC) in the tadalafil 40 mg group compared to the placebo group and the groups that used lower doses of tadalafil.

Patients (N = 357) from the placebo-controlled study entered a non-controlled long-term extension study. Of these, 311 patients have been treated with tadalafil for at least 6 months and 182 for 1 year (median exposure 356 days; range 2 days to 415 days). The survival rate in the extension study was 96.5 per 100 patient years.

1.2.2.4 Summary of safety profile

The most commonly reported adverse reactions, occurring in ≥ 10% of patients in the tadalafil 40 mg treatment arm, were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharyngitis and pain in extremity. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age. In the pivotal placebo-controlled study of tadalafil for the treatment of PAH, a total of 323 patients were treated with tadalafil at doses ranging from 2.5 mg to 40 mg once daily and 82 patients were treated with placebo. The duration of treatment was 16 weeks. The overall frequency of discontinuation due to AEs was low (tadalafil 11%, placebo 16%). Of the patients who completed the pivotal study, 357 entered a long-term extension study. Doses studied were 20 mg and 40 mg once daily.

1.2.3 Selexipag

Selexipag is approved for the treatment of PAH in the US, the European Union, and an increasing number of other countries.

More detailed information on selexipag can be found in the IB [Selexipag IB].

1.2.3.1 Nonclinical results

Selexipag is an orally available non-prostanoid prostacyclin receptor agonist. Whilst active by itself, selexipag is hydrolyzed to an active metabolite with prolonged terminal half-life and a high selectivity for the prostacyclin receptor. Selexipag and its metabolite possess anti-fibrotic, anti-proliferative, and anti-thrombotic activity. Oral selexipag is effective in an animal model of PAH, improving hemodynamic and structural factors leading to increased survival. Selexipag seems to induce minimal or no tachyphylaxis in rats.

1.2.3.2 Clinical pharmacology

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

1.2.3.3 Clinical efficacy

In the multicenter, double-blind, placebo-controlled event-driven Phase 3 clinical trial GRIPHON, conducted in 1156 patients with PAH, selexipag demonstrated a clinically and statistically significant 40% risk reduction compared to placebo in the occurrence of a first morbidity/mortality event up to end of treatment (EOT) + 7 days (hazard ratio for selexipag versus placebo 0.60, 99% CI: 0.46–0.78, 1-sided unstratified log-rank $P < 0.0001$). Results of all supportive analyses on the primary endpoint were consistent with that of the main analysis, and the observed treatment effect was also consistent across subgroups (PAH etiology, region, ethnicity, gender, age, WHO FC, and – most important in the setting of the present triple combination study – baseline PAH background medication) [Sitbon 2015, Selexipag IB].

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

1.2.3.4 Summary of safety profile

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

and 7.1%, respectively). A total of 31.7% of patients in the selexipag group and 37.1% in the placebo group had at least one AE leading to discontinuation of study treatment. Other than prostacyclin-associated AEs, most of the AEs that led to discontinuation of study treatment were SAEs associated with underlying PAH disease.

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

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

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

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

Importantly, in the GRIPHON study there were no additional safety and tolerability findings in those patients receiving selexipag on top of both an ERA and a PDE-5i.

1.3 Purpose and rationale of the study

Recent guidelines for the treatment of PAH [Galiè 2013] recommended sequential combination therapy in patients with an inadequate clinical response to initial monotherapy. However, based on the recent results of the AMBITION study [Galiè 2015a], initial dual combination therapy with an ERA and a PDE-5i is emerging as a potential new standard of care in newly diagnosed PAH patients [Galiè 2015b].

To date, only one pilot study has investigated initial triple combination therapy [Sitbon 2014], showing dramatic improvements in all relevant variables such as WHO FC, 6MWD, mPAP, cardiac index, and PVR. Although the study was small (n = 18), non-controlled, and used different drugs than in the present study (in particular, intravenous

epoprostenol as the drug acting on the prostacyclin pathway), it suggests that initial triple therapy in PAH may be beneficial and safe.

With the availability of selexipag, it is possible to investigate a triple oral therapy regimen. Data from the GRIPHON trial suggest that selexipag is efficacious and safe irrespective of whether or not subjects are already receiving other PAH drugs [Sitbon 2015, Selexipag IB]. In fact, the majority of the patient population in GRIPHON was prevalent and thus already being treated with an ERA and/or a PDE-5i at baseline.

The above-mentioned triple therapy data from the GRIPHON trial [Sitbon 2015, Selexipag IB] and the pilot study [Sitbon 2014] provide a rationale for the present study. The purpose is to investigate whether an initial triple oral treatment regimen combining an ERA, a PDE-5i, and selexipag adds significant efficacy benefit while being safe and well tolerated, as compared to an initial dual oral treatment regimen with an ERA and a PDE-5i [Galiè 2015a].

Given the extensive and long-term controlled efficacy and safety data available with all 3 study treatments (including triple combination used in many subjects in the GRIPHON study) and the careful follow-up of subjects mandated by this protocol, the benefit/risk assessment supports the current study.

2 STUDY OBJECTIVES

2.1 Primary objective

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.

2.2 Secondary objectives

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 cardio-pulmonary hemodynamics (other than PVR), exercise capacity, disease severity, disease progression events, safety, and tolerability.

2.3 Exploratory objectives

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.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

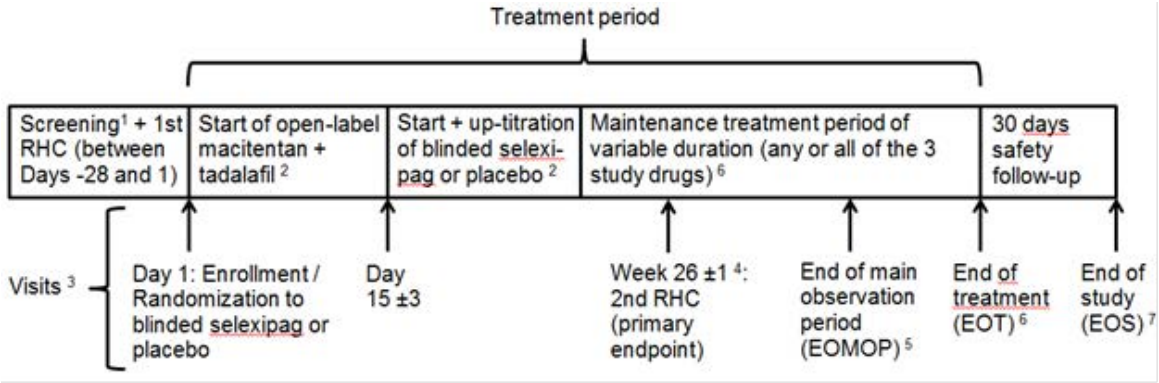
This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel group, Phase 3b, efficacy and safety study comparing a triple oral regimen (macitentan, tadalafil, selexipag) with a dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with PAH.

This study uses a group sequential design, with one interim analysis planned when approximately one third of the subjects have completed their Week 26 PVR assessment (primary endpoint) or prematurely discontinued the study.

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 FC at baseline (I/II versus III/IV). The study will be conducted at approximately 75 sites in approximately 20 countries. Randomization will proceed until the required number of subjects has been reached. It will be competitive across participating sites. Actelion may replace sites with no subject enrollment.

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 (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] Study treatment initiation scheme: See Section 5.1.3.

[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.

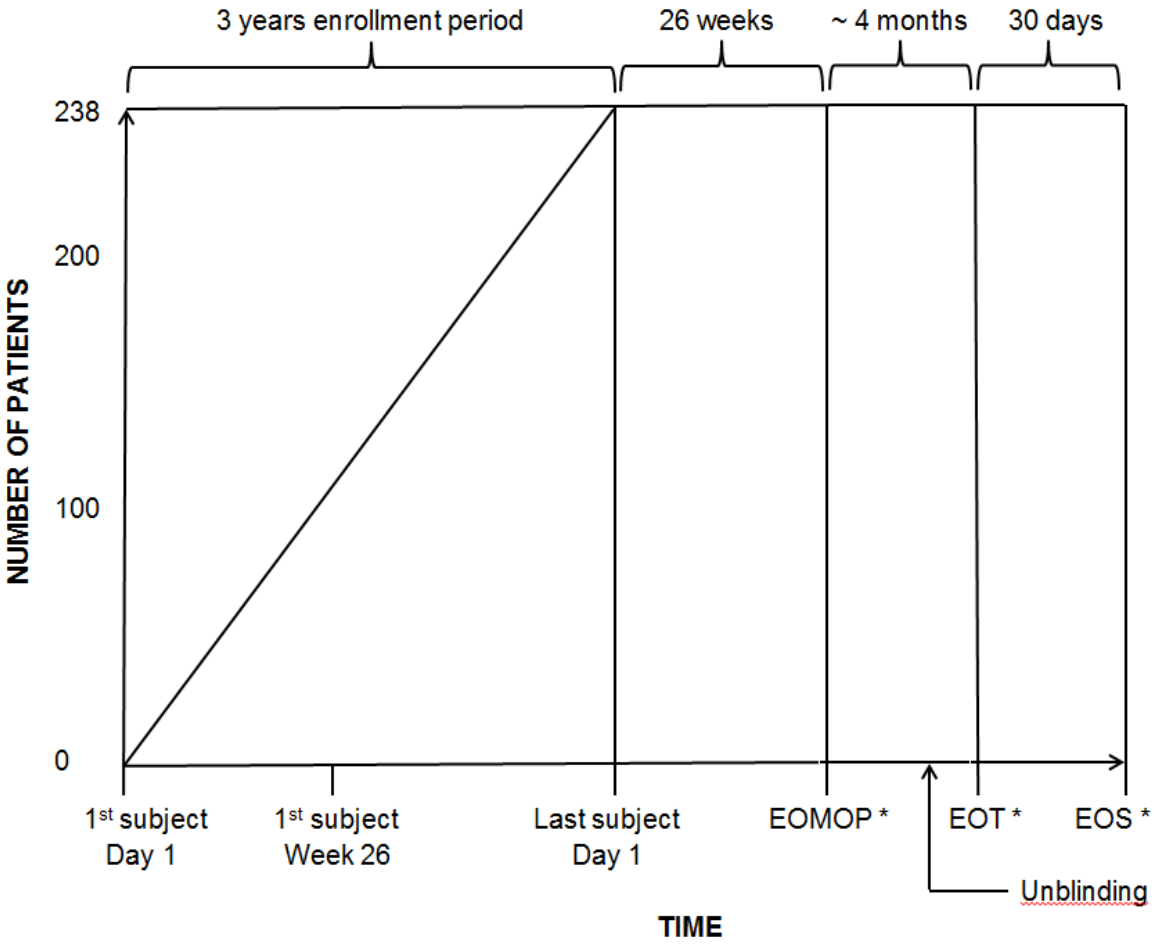
[4] If double-blind treatment (selexipag/placebo) is discontinued before Week 26: The Week 26 assessments should be done either at Week 26 or before start of rescue therapy (prostacyclin, prostacyclin analog, or prostacyclin receptor agonist), whichever is first.

[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 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 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.

Figure 2 Planned duration (study level)



* See Figure 1 for abbreviations and definitions

No sub-studies are planned.

3.2 Study design rationale

The rationale for the selected treatment groups is described in Section 1.3. The double-blind design is required to minimize any bias. Stratification by region and baseline WHO FC is justified by the fact that these variables had a major impact on PVR (primary endpoint) in previous trials, in particular in the hemodynamic sub-study of Actelion's SERAPHIN trial (AC-055-302) with macitentan.

The use of a group sequential design is justified by the absence of prior data on the potential clinical benefit of a triple versus a dual oral combination therapy. The interim analysis is

therefore designed as a futility analysis to prevent continuing the trial and exposing subjects to unnecessary burden if it is unlikely to demonstrate a relevant treatment difference.

A maximum of 28 days for screening is considered an acceptable balance between granting sufficient time to conduct all assessments and not delaying treatment start for too long.

Initiating all 3 study treatments within 2 weeks is a pragmatic balance between a true initial triple therapy approach and the need to carefully monitor subject safety during this phase. The rules for up-titration of selexipag [Section 5.1.3] are very similar to those used in the GRIPHON trial [Sitbon 2015, Selexipag IB].

The primary endpoint (PVR) is determined at Week 26 because it is expected that during the first 26 weeks the 3 study treatments have sufficient time to exert a treatment effect.

It is planned that Actelion will provide all 3 study treatments until approximately 10 months after the last subject has been enrolled (EOT). All subjects should continue the study until EOS, irrespective of whether they are receiving 3, 2, 1, or no study treatments up to EOT, and irrespective of any other PAH therapy administered. Consequently, the total study duration for a subject will vary between approximately 11 months and approximately 4 years, depending on the timepoint at which the subject is enrolled and the enrollment rate (assumed enrollment period is 3 years). The reasons for keeping subjects in the study beyond Week 26 (primary endpoint) are (1) to allow investigators to make informed decisions regarding any post-study therapy once the result of the primary analysis and study treatment allocation for each patient is known (approximately 1 month prior to EOT), (2) to assess some of the secondary and exploratory efficacy and safety endpoints requiring longer observation periods. One of the aims of this study is to explore various disease severity and clinical outcome endpoints. A traditional clinical worsening endpoint does not appear feasible in a triple combination setting (too few events).

3.3 Study committees

The following study committees will be established, each governed by a separate charter:

- Steering Committee (SC) - to advise on the study protocol, oversee the conduct of the study, contribute to interpretation of the results, and support publications.
- Clinical Events Committee (CEC) - to adjudicate the disease progression events.
- IDMC - to safeguard the interests of subjects by monitoring safety, tolerability, and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted at the highest scientific and ethical standards. The IDMC will be fully operational prior to enrollment of the first subject into the study.

- Independent Liver Safety Data Review Board (ILSDRB) - to provide advice regarding serious hepatic events of the study subjects. The ILSDRB is an external expert committee of hepatologists.

4 SUBJECT POPULATION

4.1 Subject population description

The target population is subjects with PAH [Simonneau 2013], as detailed in Sections 4.3 and 4.4.

4.2 Rationale for the selection of the study population

The minimum PVR is 480 dyn·sec/cm^5 (6 WU) in order to exclude mild PAH in a study investigating an aggressive treatment approach, i.e., initial triple therapy. Furthermore, with the change in PVR from baseline to Week 26 being the primary endpoint, subjects with an elevated baseline PVR may have a higher chance of a PVR improvement.

The minimum 6MWD is 50 m in order to ensure a baseline value is available, which is needed for several of the secondary and exploratory efficacy endpoints. This avoids imputation of missing values in subjects who can hardly walk or not walk at all.

The upper age limit is set to 75 years in order to exclude subjects with a potentially uncertain or atypical PAH diagnosis due to co-morbidities. For the same reason, subjects with conditions such as permanent atrial fibrillation, lung diseases indicative of PH etiologies other than PAH, and presence of multiple risk factors for heart failure with preserved ejection fraction are excluded.

Exclusion of the remaining concomitant diseases and therapies listed below is based on the prescribing information or other background information for one or more of the 3 study treatments [Macitentan IB, Adcirca SmPC, Adcirca USPI, and Selexipag IB].

4.3 Inclusion criteria

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

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:
   - mPAP ≥ 25 mmHg.
   - PAWP or LVEDP ≤ 15 mmHg.

- PVR ≥ 480 dyn·sec/cm^5 (≥ 6 WU).
- 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 [Simonneau 2013]:
   - 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. 6MWD ≥ 50 m at screening.
7. Women of childbearing potential [defined in Section 4.5.1] 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 [defined in Section 4.5.2] 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.

4.4 Exclusion criteria

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

1. Any PAH-specific drug therapy (e.g., any ERA, 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. SBP < 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 (PVOD).
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 (NAION).
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.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

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

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

4.5.2 Acceptable methods of contraception

Women of childbearing potential as defined in Section 4.5.1 must use reliable contraception from screening up to 1 month following discontinuation of the last study treatment. Reliable contraception must be started at least 11 days prior to Day 1. The methods of contraception used (including non-pharmacological methods) must be recorded in the electronic Case Report Form (eCRF) at every visit.

Europe and other areas outside of Australia and North America

Use of at least one of the following methods is regarded as reliable contraception:

1. Oral, implantable, transdermal, or injectable hormonal contraceptives or intrauterine devices, *or*

2. True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject, *or*

3. Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to screening), *or*

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

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

Australia

In females of childbearing potential, pregnancy should be excluded before the start of treatment and prevented thereafter by the use of two reliable methods of contraception. If necessary, patients should discuss with their doctor or gynecologist which methods would be most suitable for them. Given the teratogenic nature of macitentan, women should not become pregnant for 3 months after discontinuation of the drug.

North America

For North America, use of one of the following options is regarded as reliable contraception:

Option 1
One method from this list:
Standard IUD (Copper T380A IUD)
Intrauterine system (LNg 20IUS: progesterone IUS)
Progesterone implant
Tubal sterilization

Option 2
One method from this list:
Estrogen and progesterone oral contraceptives ("the pill")
Estrogen and progesterone transdermal patch
Vaginal ring
Progesterone injection
PLUS one method from this list:
Male condom
Diaphragm with spermicide
Cervical cap with spermicide

Option 3
One method from this list:
Diaphragm with spermicide
Cervical cap with spermicide
PLUS one method from this list:
Male condom

Option 4
One method from this list:
Partner's vasectomy
PLUS one method from this list:
Male condom
Diaphragm with spermicide
Cervical cap with spermicide
Estrogen and progesterone oral contraceptives ("the pill")
Estrogen and progesterone transdermal patch
Vaginal ring
Progesterone injection

IUD, intrauterine device; IUS, intrauterine system.

4.6 Medical history

Relevant medical history as defined in Section 7.1.3 must be recorded in the eCRF.

5 TREATMENTS

5.1 Study treatment

Study treatments are macitentan, tadalafil, and selexipag/placebo. Details and references are provided in Section 1.2.

5.1.1 Investigational treatment: description and rationale

The investigational group will receive the following:

- Macitentan oral tablet, 10 mg once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF).
- Tadalafil 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). Exceptions from the twice daily dosing regimen are described in Section 5.1.3.

The doses are in accordance with the IB for macitentan [Macitentan IB], the product labeling for tadalafil [Adcirca SmPC, Adcirca USPI], and the IB for selexipag [Selexipag IB].

5.1.2 Comparator treatment: description and rationale

The comparator group will receive the following:

- Macitentan oral tablet, 10 mg once daily (preferably always in the morning or always in the evening; to be recorded in the eCRF).
- Tadalafil 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). Exceptions from the twice daily dosing regimen are described in Section 5.1.3.

The doses are in accordance with the IB for macitentan [Macitentan IB], the product labeling for tadalafil [Adcirca SmPC, Adcirca USPI], and the IB for selexipag [Selexipag IB].

5.1.3 Study treatment administration

The 3 study treatments are administered as follows:

- Day 1: Start of open-label macitentan 10 mg once daily and open-label tadalafil 20 mg once daily.
- Day 8 ± 3: Tadalafil dose increase to 40 mg once daily (in subjects with mild or moderate renal impairment, defined as creatinine clearance > 30 and

≤ 80 mL/min/1.73 m^2, tadalafil up-titration to 40 mg once daily should be based on individual tolerability [Adcirca SmPC, Adcirca USPI]).

- Day 15 ± 3: Start of double-blind selexipag or placebo, see details below. Double-blind treatment should be started even in subjects who had to previously discontinue one or both of the other study treatments.

The starting dose of double-blind selexipag or placebo on Day 15 ± 3 is 200 µg twice daily (in the morning and in the evening). The dose is up-titrated in increments of 200 µg twice daily, usually at weekly intervals [see Table 2], until either a maximum dose of 1600 µg twice daily is reached or adverse pharmacological effects that cannot be tolerated or medically managed are experienced, whichever is first. In the event of adverse effects typical of prostanoid therapy, it is recommended not to discontinue double-blind treatment because these effects are usually transient or manageable with symptomatic treatment. If a dose that cannot be tolerated is reached, the dose should be reduced to the previous dose level.

The goal of the titration is to identify the individually appropriate dose for each subject (the maximum tolerated dose [MTD]) to be used during the maintenance treatment period, i.e., after titration has been completed. The MTD is defined as the first dose used after the Week 12 visit. Later dose changes are at the discretion of the investigator, i.e., dose adjustments of selexipag/placebo (up to the maximum dose of 1600 µg twice daily) are allowed at any time after reaching the MTD. The date and dose at every dose change are recorded on a dedicated page in the eCRF.

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

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

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

Table 2 Double-blind up-titration scheme up to the Week 12 visit

Duration (Study Days, all ± 3)	Dose regimen[1, 2, 3]	
Day 15 to Day 21	200 µg twice daily	(1 tablet twice daily)
Day 22 to Day 28	400 µg twice daily	(2 tablets twice daily)
Day 29 to Day 35	600 µg twice daily	(3 tablets twice daily)
Day 36 to Day 42	800 µg twice daily	(4 tablets twice daily)
Day 43 to Day 49	1000 µg twice daily	(5 tablets twice daily)
Day 50 to Day 56	1200 µg twice daily	(6 tablets twice daily)
Day 57 to Day 63	1400 µg twice daily	(7 tablets twice daily)
Day 64 to Week 12 visit	1600 µg twice daily	(8 tablets twice daily)

[1] Or maximum tolerated dose. The indicated doses are target doses if previous dose level was tolerated or if tolerability issues were addressed by down-titration.

[2] When titrating up or down, it is recommended to take the first new dose in the evening.

[3] Exceptions from the twice daily dosing regimen are described in Section 5.1.3.

For all 3 study treatments, tablets are to be taken orally, with or without food. Tolerability may be improved when taken with food. The tablets should not be split, crushed or chewed, and are to be swallowed with some water. If a dose has been missed, the subject must take it as soon as possible (unless the next dose is within the next 6 hours), and then take the next dose at the next scheduled time.

5.1.4 Treatment assignment

At Screening, subjects will be assigned a study-specific subject number by the Interactive Response Technology (IRT) system. This number is kept throughout the study and is the main subject identifier. Note: In case of re-screening, the original number will also be used the second time.

At the randomization visit, after having confirmed the eligibility of the subject and prior to the start of study treatment, the subject will be randomized. The IRT system will assign a randomization number to the subject (in addition to the subject number mentioned above), and assign the treatment container number which matches the treatment arm assigned by the randomization list to the randomization number.

The randomization list is generated by an independent Contract Research Organization (CRO), Almac.

Randomization will be done in a 1:1 ratio. Stratification will be by region (North America versus rest of world) and WHO FC at baseline (I/II versus III/IV).

5.1.5 Blinding

The study will be performed in an open-label fashion for macitentan and tadalafil.

The study will be performed in a double-blind fashion for selexipag and its matching placebo. Selexipag and its matching placebo are indistinguishable and all treatment kits will be packaged in the same way.

The investigator and study staff, the subjects, the monitors, Actelion staff, and CROs involved in the conduct of the study will remain blinded to the study treatment until database closure. Actelion staff responsible for clinical trial supply distribution will need to be unblinded to ensure adequate distribution of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file and they will not take part in any Clinical Trial Team meetings after study set-up has been completed.

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

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure (following EOMOP) in accordance with Actelion Standard Operating Procedures (SOPs). The treatment group allocation (selexipag or placebo) will be provided to study sites approximately 1 month prior to EOT.

5.1.6.2 Unblinding for interim analyses

A formal interim analysis is planned. In addition, an IDMC will review efficacy, safety and tolerability data at regular time intervals. The access to randomization information will in any case be limited to the independent Statistical Analysis Center (SAC) which will prepare all outputs for the interim analysis and the analyses required for the IDMC. The SAC will be represented by an independent statistician.

5.1.6.3 Unblinding for suspected unexpected serious adverse reactions

When a reported SAE qualifying as a suspected unexpected serious adverse reaction (SUSAR) for any of the administered study treatments occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment only if the reported SAE is assessed as related to blinded study medication (selexipag or placebo) and if this event is not listed in Selexipag IB reference safety information section [Selexipag IB] or does not represent an event that is PAH disease related [see Section 10.2.5]. The randomization code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information will be anonymized and

provided to Actelion Global Drug Safety, regulatory authorities, and IRBs/IECs only. SUSARs will be reported to investigators in a blinded fashion with regard to blinded study medication.

No systematic unblinding of treatment assignment of blinded study medication is required if the reported SUSAR qualifies for the open-label study medication(s), macitentan or tadalafil.

5.1.6.4 Emergency procedure for unblinding

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

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

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

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

5.1.7.1.1 Study treatment packaging

Study treatment is provided as tablets for all 3 study treatments. All 3 study treatments are provided in childproof kits.

5.1.7.1.2 Study treatment labeling

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

5.1.7.2 Study treatment distribution and storage

The investigator is responsible for safe and proper handling and storage of the study treatments at the investigational site, and for ensuring that the study treatments are administered only to subjects enrolled in the study and in accordance with the protocol. Study treatments must be kept in a locked cabinet or room, which can be accessed only by the pharmacist, the investigator, or another duly designated person.

Study treatment supplies must be stored according to the conditions specified on the container labels.

5.1.7.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects will be asked to return all used, partially used, and unused study treatment (including the kits) at each visit. The protocol-mandated study treatment dispensing/return procedures may not be altered without prior written approval from Actelion. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.7.4 Study treatment return and destruction

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused treatment kits, which will be sent to the warehouse, where Actelion or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by Actelion or the deputy, and written permission for destruction has been obtained from Actelion.

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

The inventory of study treatment dispensed and returned (i.e., study treatment accountability) must be performed by the study staff on the day of the subject visit and before dispensing further study treatment. It is recorded on the investigational medicinal product dispensing and accountability log and checked by the Clinical Research Associate (CRA) during site visits and at the end of the study. The study treatment accountability log will include at least the following information for each study treatment unit (kit) dispensed to the subject, for each of the 3 study treatments:

- Dispensed kit number
- Date dispensed / Number of tablets dispensed (pre-populated in eCRF)
- Date returned / Number of tablets returned

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

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

5.1.8.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance must be calculated at each visit using the formula below, separately for the 3 study treatments:

Compliance =
[(number of tablets dispensed - number of tablets returned) / total number of tablets that should have been taken during the respective period between 2 visits] × 100

During the study, compliance is expected to be between 80% and 120%. If out of range value(s) are noticed for any of the 3 study treatments (from study treatment accountability), they will be considered as a protocol deviation. The investigator must check with the subject the reasons for this non-compliance and discuss actions to be taken to avoid recurrence at the next visit.

Compliance of selexipag will not be assessed for the period up to the Week 12 visit.

5.1.9 Study treatment dose adjustments and interruptions

Any of the 3 study treatments may be temporarily interrupted if required due to an AE, a tolerability issue, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Interruptions of study treatments should be kept as short as possible. Interruptions must be for less than 4 consecutive weeks; longer interruptions must lead to permanent discontinuation of the respective study treatment(s). Study-specific criteria for interruption of study treatment are described in Section 5.1.11.

Dose adjustments are permitted for tadalafil (e.g., reduction from 40 to 20 mg once daily) and double-blind selexipag or placebo. No dose adjustment is possible for macitentan.

Any interruption of 3 days or more of blinded selexipag/placebo treatment will require new up-titration. Subjects will start with one tablet (200 µg) twice daily. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg increments up to the subject's maximum dose achieved before interruption. The frequency of dose increments will be based on the medical judgment of the investigator, considering the subject's tolerability to selexipag/placebo prior to its interruption.

If study treatment intake is interrupted or the dose adjusted by the subject for any reason, she/he must immediately inform the investigator.

Study treatment dose adjustments / interruptions must be recorded in the eCRF.

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue any of the 3 study treatments may be made by the subject, the investigator, or Actelion. The main reason for discontinuation of study treatment and whether it is the decision of the subject, the investigator, or Actelion is documented in the eCRF. However, the subject is not obliged to provide a reason.

A subject has the right to prematurely discontinue any of the 3 study treatments at any time by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study, see Section 9.2).

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

Any of the 3 study treatments may be discontinued in response to an AE, lack of efficacy (including disease progression, treatment failure, worsening of subject's condition), a protocol deviation (including eligibility failure, non-compliance with study requirements), a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons.

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

A subject who prematurely discontinues all study treatments and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

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

For more details see the prescribing information or other background information for the 3 study treatments [Macitentan IB, Adcirca SmPC, Adcirca USPI, local prescribing information for tadalafil, Selexipag IB].

A) Pregnancy

If a female subject becomes pregnant after study start (i.e., signing of informed consent) and up to 1 month following discontinuation of the last study treatment, a Pregnancy Form

must be completed [see Section 10.3]. Therapy with all study treatments must be discontinued and the investigator should arrange for any PAH-specific therapy as needed [ESC Guidelines]. In the event of pregnancy with abortion, the investigator should discuss the impact on study treatment with Actelion.

B) Liver aminotransferases abnormalities

Interruption of study treatment
Study treatment with macitentan must be interrupted in the following case:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and < 8 × ULN

Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase within one week. If AST and/or ALT elevation is confirmed, continue to monitor aminotransferases, total and direct bilirubin, and alkaline phosphatase levels weekly until values return to pre-treatment levels or within normal ranges. If the aminotransferase values return to pre-treatment levels or within normal ranges, reintroduction of macitentan can be considered.

Reintroduction of macitentan after treatment interruption should only be considered if the potential benefits outweigh the potential risks and when liver aminotransferase values are within pre-treatment levels or within normal ranges. The advice of a hepatologist is recommended.

Liver aminotransferase levels must be checked within 3 days after reintroduction, then again after a further 2 weeks and thereafter at monthly intervals.

Permanent discontinuation of study treatment
Study treatment with macitentan must be stopped and its reintroduction is not to be considered in any of the following cases:

- Aminotransferases ≥ 8 × ULN.
- Aminotransferases ≥ 3 × ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever). However, the investigator may consider reintroduction of macitentan treatment (as described in the paragraph 'Interruption of study treatment' above) if he/she judges the symptom(s) to be unrelated to the elevated aminotransferase levels.
- Aminotransferases ≥ 3 × ULN and associated increase in total bilirubin ≥ 2 × ULN.

Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (e.g., acetaminophen-related liver toxicity) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferases abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs [see Section 10].

An ILSDRB provides ongoing assessment and advice regarding serious hepatic events that require further evaluation during the study.

C) Severe hepatic impairment

If liver impairment is suspected, a clinical assessment of severity (e.g., Child-Pugh score) should be performed. If the investigator becomes aware that a patient has developed moderate hepatic impairment (e.g., Child-Pugh B) at any time during the study, then it is the responsibility of the investigator to evaluate the benefit/risk of keeping the patient on any or all of the 3 study treatments.

If a patient develops severe hepatic impairment (e.g., Child-Pugh C), the study drugs macitentan, tadalafil, and selexipag/placebo must be discontinued.

Assessment of Child-Pugh score is not a mandatory study assessment.

D) Severe renal impairment

Study treatment with tadalafil must be discontinued in the event of severe renal impairment (estimated creatinine clearance $\leq$ 30 mL/min/1.73 m^2).

E) Pulmonary edema due to PVOD

If a subject develops pulmonary edema due to PVOD consider discontinuation of the 3 study treatments, and consult the background information [Macitentan IB, Adcirca SmPC, Adcirca USPI, local prescribing information for tadalafil, Selexipag IB] regarding the risk of pulmonary edema.

F) Vision disorder

Study treatment with tadalafil must be discontinued in case of loss of vision in one or both eyes because of NAION.

G) Hemoglobin abnormalities

In case of hemoglobin decrease from baseline* of > 20 g/L during study treatment with macitentan, a re-test must be performed within 10 days; additional (local) laboratory evaluations may include, but are not limited to, any of the following:

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

Study treatment with macitentan should be temporarily interrupted if clinically mandated based on the investigator's judgment, or in any of the following situations (unless clearly unrelated to macitentan, e.g., hemoglobin decrease due a bleeding event):

- A decrease in hemoglobin to < 80 g/L (< 4.9 mmol/L),
- A decrease in hemoglobin from baseline* of > 50 g/L,
- The need for transfusion.

Reintroduction of study treatment with macitentan may be considered if hemoglobin recovers, i.e., if the hemoglobin value returns to above the lower limit of the normal range or to a value close to that at baseline, and if the potential benefits of reintroducing macitentan outweigh the potential risks.

H) Start of a CYP3A4 or CYP2C8 inducer or inhibitor

Study treatment with macitentan and tadalafil must be discontinued if a strong CYP3A4 inducer or inhibitor is started during study treatment with macitentan and/or tadalafil.

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

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

In case of concomitant administration of a moderate inducer of CYP2C8 (e.g., rifampicin), dose adjustment of selexipag/placebo may be required because of drug-drug interactions.

* Baseline hemoglobin: last value obtained prior to first intake of macitentan study treatment.

A drug-drug interaction study showed that rifampicin did not lead to a relevant change in exposure to selexipag, whereas exposure to the active metabolite decreased by half [Selexipag IB].

I) Start of doxazosin and/or organic nitrates

Study treatment with tadalafil must be discontinued if doxazosin and/or any organic nitrate is started during treatment.

J) Start of another PAH-specific drug

Subjects remain in the study irrespective of whether they are receiving 3, 2, 1, or no study treatments, even if another PAH drug is started.

Study treatment with macitentan must be discontinued if another ERA is started concurrently during macitentan treatment.

Study treatment with tadalafil must be discontinued if another PDE-5i or soluble guanylate cyclase stimulator is started concurrently during tadalafil treatment.

Study treatment with double-blind selexipag/placebo must be discontinued if another prostacyclin, prostacyclin analog, or prostacyclin receptor agonist is started during treatment, e.g., as rescue therapy. Details are described in Section 5.2.5.

K) Hyperthyroidism or hypothyroidism

In the event of clinical suspicion or manifestation of hyperthyroidism or hypothyroidism, thyroid function markers including thyroid stimulating hormone, free triiodothyronine (T3), and free thyroxine (T4) levels must be monitored by the investigator/delegate and appropriate measures according to local clinical practice should be implemented.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to the start of study (i.e., signing of informed consent).

A study-concomitant therapy is any treatment that is administered at any time between the start of study (i.e., signing of informed consent) and EOS.

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).

5.2.2 Reporting of previous/concomitant therapy in the eCRF

All concomitant therapy (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines, and also cardio-pulmonary rehabilitation programs based on exercise) will be recorded in the eCRF. Previous therapy will be recorded in the eCRF if discontinued less than 28 days prior to the start of study (i.e., signing of informed consent).

For both previous and concomitant therapy, the generic name, start/end dates of administration (as well as whether it was ongoing at key timepoints such as EOS), route of administration, dose, and indication will be recorded in the eCRF.

Single-dose administration of a drug for vasoreactivity testing during RHC should NOT be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

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

Cardio-pulmonary rehabilitation programs based on exercise, started after the Week 26 visit.

5.2.4 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 [see Section 5.2.5]. 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. See also Section 5.1.11, paragraph J.
- 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.

PAH-specific drugs other than the 3 study treatments are forbidden in order to minimize confounding effects on the outcome. Organic nitrates and doxazosin are forbidden in order to comply with the prescribing information of tadalafil, strong CYP3A4 inducers and inhibitors are forbidden during treatment with macitentan and/or tadalafil in order to comply with the background information for macitentan and tadalafil [Macitentan IB, Adcirca SmPC, Adcirca USPI, local prescribing information for tadalafil]. Strong CYP2C8 inhibitors are forbidden during treatment with selexipag/placebo because of drug-drug interactions (as described in Selexipag IB).

Section 5.1.11 describes actions to be taken if a subject takes a forbidden concomitant therapy.

5.2.5 Rescue therapy

In the event of documented worsening of PAH, it is permitted to use prostacyclin, prostacyclin analogs, or prostacyclin receptor agonists as rescue therapy, in parallel to discontinuation of double-blind study treatment. Start of rescue therapy and discontinuation of double-blind selexipag or placebo may overlap in order to ensure sustained efficacy during the transition. Subjects starting rescue therapy remain in the study until EOS, irrespective of whether they are receiving any of the 3 study treatments.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

A traditional morbidity/mortality endpoint (as defined in Actelion's SERAPHIN and GRIPHON trials) does not appear feasible due to the expected low event rates in the setting of the present study (subjects receiving at least two PAH-specific drugs). Therefore, the trial is designed as a pilot study (with PVR as the primary endpoint) that will explore various disease severity and clinical outcome endpoints.

For the purpose of this study, baseline is defined as the last available assessment from the screening and Day 1 visits.

6.1.1 Primary efficacy endpoint

The primary endpoint is the ratio of Week 26 to baseline PVR.

RHC is the standard approach for the initial confirmation of the presence of PH, for establishing the specific diagnosis (e.g., PAH), determining the severity of PH, and for guiding therapy. PVR as determined by RHC is needed to obtain an objective judgment on the hemodynamic response to treatment and to improve management. Likewise, PVR is associated with disease severity and correlates with mortality. An increase in PVR leads to right ventricular overload, hypertrophy, dilatation, and eventually to right ventricular failure and death.

6.1.2 Secondary efficacy endpoints

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. Absence of worsening from baseline to Week 26 in WHO FC.
4. Changes from baseline to Week 26 in RHC variables other than PVR (mPAP, cardiac index, total pulmonary resistance, mean right atrial pressure (mRAP), venous oxygen saturation).
5. Time from randomization to the first disease progression event up to EOMOP + 7 days (adjudicated by the 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).

6.1.3 Exploratory efficacy endpoints

1. Changes in NT-proBNP, 6MWD, and WHO FC from baseline to all regular collection timepoints up to EOMOP.
2. Unsatisfactory clinical response defined as % of subjects meeting at least one of the following three conditions [adapted from McLaughlin 2013], analyzed at every scheduled visit from Week 26 up to EOMOP:
    a. WHO FC III or IV.
    b. 6MWD ≤ 440 m AND NT-proBNP ≥ 3 × ULN.
    c. Clinical worsening event as defined under secondary efficacy endpoint 5, at any time up to the respective visit.
3. Number of treatment goals (score 0 = no or 1 = yes per goal, i.e., total score 0–5, with 5 representing the best treatment outcome) met at Week 26 [adapted from McLaughlin 2013]:
    - WHO FC I or II.
    - Cardiac index > 3 L/min/m^2.
    - mRAP < 8 mmHg.
    - 6MWD > 440 m.
    - NT-proBNP < 3 × ULN.
4. Number of treatment goals as defined in exploratory efficacy endpoint 3 but using > 2.5 L/min/m^2 as an alternative cutoff for cardiac index.

5. Number of treatment goals as defined in exploratory efficacy endpoint 3 but using < 1800 pg/mL as an alternative cutoff for NT-proBNP [Nickel 2012].

6.2 Safety endpoints

The following safety endpoints will be used:

- Treatment-emergent AEs.
- AEs leading to premature discontinuation of any of the 3 study treatments.
- Treatment-emergent SAEs.
- Treatment-emergent deaths.
- Treatment-emergent marked laboratory abnormalities.
- Change from baseline in laboratory variables.
- Change from baseline in vital signs.

The safety endpoints will be analyzed for the following time periods:

- From Day 1 until EOMOP.
- From Day 1 until start of double-blind treatment (selexipag/placebo).
- From start until discontinuation of macitentan study treatment (or until EOMOP, whichever is first) + 30 days safety follow up.
- From start until discontinuation of tadalafil study treatment (or until EOMOP, whichever is first) + 30 days safety follow up.
- From start until discontinuation of double-blind treatment (or until EOMOP, whichever is first) + 30 days safety follow up.
- From EOMOP until EOT plus 30 days safety follow-up.
- The 30 days safety follow-up.

6.3 Biomarker endpoints

Based on nonclinical data [Gomez-Arroyo 2015], it is hypothesized that selexipag may have a beneficial effect on circulating biomarkers involved in right ventricular function and structure. Therefore, changes in such biomarkers from baseline to Week 26 will be explored. The list of biomarkers to be measured after the end of the study will be based on the latest scientific evidence regarding right ventricular function and structure at the time of laboratory analysis. No genetic testing of any kind will be performed [see Section 7.3.7.2].

7 STUDY ASSESSMENTS

Signed written informed consent is to be obtained prior to any study-mandated procedure.

All study assessments (at scheduled or unscheduled visits) are performed by qualified study staff members (medical, nursing, or specialist technical staff), and are recorded in the eCRF (except the central laboratory assessments, see Section 7.3.7).

If the principal investigator (PI) delegates any study procedure/assessment for a subject to an external facility, he/she should inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains the responsibility of the PI.

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

7.1 Screening/baseline assessments

Table 1 summarizes which assessments are performed at which visit.

For subjects who fail screening, only data related to eligibility criteria, demographics and baseline characteristics are collected in the eCRF.

7.1.1 Eligibility criteria

Inclusion and exclusion criteria as listed in Sections 4.3 and 4.4.

7.1.2 Demographic and baseline characteristics

- Age, gender, height, weight.
- Race (if allowed by local regulations).
- PAH etiology (classification), date of initial PAH diagnosis.

7.1.3 Medical history

The subject's relevant medical history up to start of study (i.e., signing of informed consent) must be recorded in the eCRF and should include, but is not limited to:

- Any chronic medical conditions (e.g., diabetes).
- Any acute medical conditions in the past 6 months.
- Any other medically important conditions.

7.1.4 Previous therapies

Previous therapies must be recorded in the eCRF [see Section 5.2.1].

7.2 Efficacy assessments

Table 1 summarizes which assessments are performed at which visit.

7.2.1 RHC

The rationale for using RHC (and PVR as the primary endpoint) is provided in Section 6.1.1.

For the RHC methodology to be used see the Actelion guidelines for RHC [Appendix 1].

The following variables are determined and entered in the eCRF:

- PVR
- Systolic pulmonary artery pressure (sPAP)
- Diastolic pulmonary artery pressure (dPAP)
- mPAP
- PAWP or LVEDP
- mRAP
- Cardiac output (CO)
- Cardiac index
- Heart rate (HR) during RHC
- Venous oxygen saturation
- Systolic systemic artery pressure (sSAP)
- Diastolic systemic artery pressure (dSAP)
- Date of the RHC

7.2.2 6-minute walk test, Borg dyspnea index

The 6-minute walk test (6MWT) [ATS Statement 2002] is a non-encouraged test which measures the distance covered over a 6-minute walk. The 'Actelion guidelines for 6MWT' [Appendix 2] must be followed. For subjects who have never performed a 6MWT previously, a training test is recommended before the qualifying test for inclusion.

The Borg dyspnea index is evaluated after each 6MWT. It rates dyspnea on a scale from '0' to '10' [Appendix 3].

7.2.3 WHO functional class

WHO FC [Appendix 4] is a classification which reflects disease severity based on symptoms.

7.2.4 Circulating biomarkers of right ventricular function and structure

Laboratory testing of circulating biomarkers of right ventricular function and structure is included in Section 7.3.7.2.

7.2.5 Other efficacy assessments

Other efficacy assessments are detailed in Section 6.1.

7.3 Safety assessments

Table 1 summarizes which assessments are performed at which visit.

7.3.1 (Serious) adverse events

The definitions, reporting and follow-up of AEs, SAEs and pregnancies are described in Section 10.

7.3.2 Contraception methods and pregnancy testing

For women of childbearing potential [Section 4.5.1], contraception methods and monthly pregnancy testing must be recorded in the eCRF.

7.3.3 Vital signs

Systolic and diastolic blood pressure and HR are measured non-invasively in the same position (e.g., supine) throughout the study.

7.3.4 Body weight

Body weight is used for the calculation of BMI (calculated as body weight in kg divided by height in m^2) and of hemodynamic indices.

7.3.5 Physical examination

Physical examination (i.e., inspection, percussion, palpation, and auscultation) is performed during the study. The observations should be reported according to body system in the eCRF as either normal or abnormal. If abnormal, this should be specified on the corresponding eCRF page. Clinically relevant findings (other than those related to PAH) that are present at study start (i.e., signing of informed consent) must be recorded on the Medical History eCRF page. Findings made after study start which meet the definition of an AE [Section 10.1.1] must be recorded on the AE page of the eCRF.

7.3.6 Concomitant therapies

Concomitant therapies must be recorded in the eCRF [see Section 5.2].

7.3.7 Laboratory assessments

7.3.7.1 Type of laboratory

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

Eligibility of subjects at Screening may alternatively be determined using local laboratory tests as long as the central laboratory kit is used in parallel. Local laboratory results alone may be sufficient in other exceptional situations (e.g., subject is hospitalized in a different hospital due to a medical emergency). Local laboratory data including the normal ranges must be entered on dedicated eCRF pages. The investigator/delegate will provide Actelion with the name, professional degree, and curriculum vitae of the director of the local

laboratory, a copy of the laboratory's certification, and the normal ranges for each laboratory test that is evaluated locally. These laboratory references must be updated whenever necessary.

Under specific circumstances (e.g., if the subject lives far from the site and cannot return every month for liver and hemoglobin testing), laboratory samples may be collected at a laboratory close to where the subject lives (satellite laboratory) or by a phlebotomy service at the subject's home, and sent to the central laboratory for analysis. In such a case, the satellite laboratory or phlebotomy service must be provided with the central laboratory sampling kits. Shipment of the samples will be organized by the satellite laboratory. If this process is implemented, the satellite laboratory must be identified prior to randomization of the subject. The supervision of the satellite laboratory remains the responsibility of the PI. The supervision of the phlebotomy service is the responsibility of Actelion.

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

Central laboratory reports will be sent to the study site. In the event of specific laboratory abnormalities (pre-defined threshold values), the central laboratory will alert Actelion and the concerned study site [Appendix 5].

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

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

7.3.7.2 Laboratory tests

In Table 1 and Section 8, the following are summarized as 'general' laboratory tests: Hematology, clinical chemistry including liver and hemoglobin tests, coagulation tests, and NT-proBNP.

Hematology

Rules for additional investigations and study treatment interruption in case of hemoglobin abnormalities are provided in Section 5.1.11.

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

Clinical chemistry

Rules for study treatment interruption in case of liver enzymes abnormalities or severe renal impairment are provided in Section 5.1.11.

The Cockcroft-Gault formula is used for estimation of the creatinine clearance: Estimated creatine clearance rate = (140 – age) × (weight in kg) × (1.23 for men and 1.04 for women), divided by serum creatinine in µmol/L.

- Aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase
- Creatinine, urea
- Uric acid (serum urate)
- Glucose
- Sodium, potassium, chloride, calcium
- Protein, albumin

Coagulation tests

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

Pregnancy test

Monthly (± 1 week) pregnancy tests are done for women of childbearing potential [as defined in Section 4.5.1]. For details, see Table 1, including footnotes.

Pregnancy reporting requirements are described in Section 10.3. Also see Section 5.1.11.

Biomarkers of myocardial stress and of right ventricular function and structure

- NT-proBNP

- Circulating biomarkers involved in right ventricular function and structure (blood samples will be stored at the central laboratory or a specialized laboratory for up to two years after the last subject's last visit and destroyed after that date. The list of biomarkers to be measured after the end of the study will be based on the latest scientific evidence regarding right ventricular function and structure at the time of laboratory analysis. No genetic testing of any kind will be performed).

8 SCHEDULE OF VISITS

For a tabulated summary of all visits and assessments described here see Table 1. For a description of the assessment methods see Section 7.

For this clinical trial, a month is defined as 30 days.

All assessments except the central laboratory results must be recorded in the eCRF.

Monthly (± 1 week) central laboratory testing of liver aminotransferases, total and direct bilirubin, and hemoglobin is mandatory throughout the study. For monthly testing, blood drawing is performed either at the study site, at a satellite laboratory close to where the subject lives, or by a phlebotomy service at the subject's home.

In women of childbearing potential [Section 4.5.1], serum pregnancy tests are performed at Screening, Week 12, Week 26, monthly (± 1 week) throughout the study, at EOMOP, EOT, and if pregnancy is suspected at any time during the study. Urine pregnancy tests are performed at the Day 1 visit and if a monthly serum test is missed. At EOS either serum or urine pregnancy tests are performed. To ensure compliance, at each visit, the study personnel must remind women of childbearing potential to perform monthly pregnancy tests and to use reliable contraception as defined for this study [Section 4.5.2]; the reminders must be documented in the hospital chart.

8.1 Screening period

It is the responsibility of the investigator to obtain written informed consent (Informed Consent Form [ICF]) from each patient participating in the study after adequate explanation of the objectives, methods, and potential benefits and hazards of the study. The ICF must be signed and dated by both parties prior to any study assessment or procedure. However, RHC data obtained at the study site within 28 days prior to Day 1 but before the study (i.e., before signed informed consent) are acceptable.

Assessments of the screening period must be performed between Day −28 and the Day 1 (enrollment/randomization) visit. Reliable contraception [defined in Section 4.5.2] must be started at least 11 days prior to Day 1.

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication). All

screening assessments should then be repeated at the time of re-screening (including signature of the ICF if the first ICF was signed more than 28 days prior to Day 1 [i.e., randomization]).

The screening period includes recording of the following [see Table 1]:

- Check of eligibility (inclusion and exclusion criteria)
- Demographics
- Medical history
- RHC
- Physical examination
- Vital signs (BP, HR)
- WHO FC
- 6MWD, Borg dyspnea index
- Central laboratory tests (general, serum pregnancy test, and biomarkers); eligibility of subjects at Screening may alternatively be determined using local laboratory tests as long as the central laboratory kit is used in parallel
- Contraceptive methods used
- Previous therapies
- AEs, SAEs

8.2 Treatment period

For monthly central laboratory testing requirements during the treatment phase see footnote 9 of the Visit and assessment schedule [Table 1].

8.2.1 Day 1 (randomization) visit

The Day 1 (randomization) visit includes recording of the following [see Table 1]:

- Vital signs (BP, HR) *
- WHO FC *
- 6MWD, Borg dyspnea index *
- Central laboratory tests (general) *
- Urine pregnancy test
- Contraceptive methods used
- Concomitant therapies
- AEs, SAEs

* Only required if the respective assessment from the screening period was obtained more than 7 days prior to the Day 1 visit.

At the end of this visit, subjects are randomized to one of the two treatment groups. Macitentan and tadalafil study treatments are dispensed to the subjects. Treatment is initiated as described in Section 5.1.

8.2.2 Day 8 visit

The Day 8 (± 3 days) visit may be performed as a phone call and includes recording of the following [see Table 1]:

- AEs, SAEs

At the end of this visit, the dose of tadalafil is increased as described in Section 5.1.

8.2.3 Day 15 visit

The Day 15 (± 3 days) visit includes recording of the following [see Table 1]:

- Physical examination
- Vital signs (BP, HR)
- Contraceptive methods used
- Concomitant therapies
- AEs, SAEs

At the end of this visit, double-blind selexipag/placebo is dispensed to the subjects. The subjects initiate treatment and up-titration (on top of ongoing study treatment with macitentan and tadalafil) as described in Section 5.1.

8.2.4 Weekly phone calls during up-titration

Weekly phone calls are performed during the up-titration phase of double-blind study treatment. They include instructing the subjects regarding the dose of double-blind study treatment and recording of the following [see Table 1]:

- AEs, SAEs

8.2.5 Week 12 visit

The Week 12 (± 1 week) visit includes recording of the following [see Table 1]:

- Physical examination
- Vital signs (BP, HR)
- WHO FC
- 6MWD, Borg dyspnea index
- Central laboratory tests (general, serum pregnancy test)
- Contraceptive methods used
- Concomitant therapies

- AEs, SAEs

At this visit, study treatments are dispensed and returned as described in Section 5.1.

8.2.6 Week 26 visit

The Week 26 (± 1 week) visit includes recording of the following [see Table 1]:

- RHC
- Physical examination
- Vital signs (BP, HR)
- WHO FC
- 6MWD, Borg dyspnea index
- Central laboratory tests (general, serum pregnancy test, and biomarkers)
- Contraceptive methods used
- Concomitant therapies
- AEs, SAEs

At this visit, study treatments are dispensed and returned as described in Section 5.1.

8.2.7 Month 12, 18, 24, 30, etc. visits

The Month 12, 18, 24, 30, etc. (± 2 weeks) visits include recording of the following [see Table 1]:

- Physical examination
- Vital signs (BP, HR)
- WHO FC
- 6MWD, Borg dyspnea index
- Central laboratory tests (general, serum pregnancy test)
- Contraceptive methods used
- Concomitant therapies
- AEs, SAEs

At these visits, study treatments are dispensed and returned as described in Section 5.1.

8.2.8 EOMOP visit

The EOMOP visit [see Section 3.1] includes recording of the following [see Table 1]:

- Physical examination
- Vital signs (BP, HR)
- WHO FC
- 6MWD, Borg dyspnea index
- Central laboratory tests (general, serum pregnancy test)

- Contraceptive methods used
- Concomitant therapies
- AEs, SAEs

At this visit, study treatments are dispensed and returned as described in Section 5.1.

8.2.9 EOT visit

The EOT visit [Section 3.1] includes recording of the following [see Table 1]:

- Physical examination
- Vital signs (BP, HR)
- WHO FC
- 6MWD, Borg dyspnea index
- Central laboratory tests (general, serum pregnancy test)
- Contraceptive methods used
- Concomitant therapies
- AEs, SAEs

At this visit, all study treatments are returned by the subjects, as described in Section 5.1.

8.2.10 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the visit and assessment schedule in Table 1.

If any post-baseline decrease in 6MWD by > 15% from the highest 6MWD obtained at or after screening is observed, accompanied by WHO FC III or IV, then both the 6MWD and WHO FC must be reassessed at an unscheduled visit after 1–21 days.

8.3 Safety follow-up

All subjects undergo a 30 days safety follow-up prior to EOS.

8.3.1 EOS visit

The EOS visit may be performed as a phone call. It is performed at the end of the safety follow-up, i.e., 30–35 days after EOT.

The EOS visit includes recording of the following [see Table 1]:

- Pregnancy test (serum or urine)
- Contraceptive methods used

- AEs, SAEs

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

Sites will be informed once the planned total subject enrollment is met. Subjects in screening (i.e., signed informed consent available but not yet randomized) at that point in time will be allowed to be randomized if they are eligible. No additional subjects may be screened. All subjects still in the study will be invited for their EOMOP visit 26 weeks after enrollment of the last subject, and for their EOT visit approximately 4 months after EOMOP.

The end of the study as a whole is the date of the last subject's EOS visit.

9.2 Premature withdrawal of subjects from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward.

The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

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

If premature withdrawal from the study occurs for any reason, the reason along with who made the decision (subject, investigator, or Actelion) is recorded in the eCRF. However, the subject is not obliged to provide a reason.

If a subject is withdrawn from the study because of withdrawal of consent, the investigator should make efforts to schedule a last appointment/phone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment/phone call will be recorded in the subjects' medical records but it will not be reported in the eCRF or SAE Form, unless the subject agrees with such reporting. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally (e.g., based on the outcome of the interim analysis) or locally. Investigators can terminate the participation of their site in the study at any time.

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

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with Actelion must promptly inform all enrolled subjects, and ensure their appropriate treatment and follow-up, as described in Section 9.2. Actelion may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

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

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

Any suspension or premature termination of the study must be discussed with the IDMC and SC.

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

At the subjects' EOT, the investigator/delegate will explain to subjects what standard treatment/medical care is necessary and available according to local regulations. Such care may include commercial PAH-specific drugs.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

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

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

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study (i.e., signing of informed consent).
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse, and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study treatment log of the eCRF.

10.1.2 Intensity of adverse events

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

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If the intensity of an AE with an onset date between informed consent signature and start of study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

A mild, moderate, or severe AE may or may not be serious [see Section 10.3.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

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

10.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatments, and reported as either related or unrelated to macitentan, tadalafil, or blinded study treatment (selexipag/placebo). The determination of the likelihood that the study treatments caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated to study design or protocol-mandated procedures

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

10.1.5 Reporting of adverse events

All AEs occurring after study start (i.e., signing of informed consent) and up to EOS must be recorded on specific AE pages of the eCRF.

10.1.6 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 Serious adverse events

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

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

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

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

10.2.2 Reporting of serious adverse events

All SAEs occurring after study start (i.e., signing of informed consent) up to EOS must be reported on AE pages in the eCRF and on an SAE form, regardless of the

investigator-attributed causal relationship with study treatment or study-mandated procedures.

10.2.3 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

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

New SAEs occurring after the 30-days follow-up period must be reported to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to any of the 3 study treatments.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to any of the study treatments (macitentan, tadalafil, or selexipag/placebo).

The SAE forms must be faxed to the Actelion drug safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

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

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to regulatory authorities, IRBs/IECs, and investigators are the background information for the 3 study treatments [reference safety information section of Macitentan IB, Adcirca USPI, reference safety information section of Selexipag IB].

The following events that are anticipated to occur in subjects with PAH will be considered as 'disease-related' and will not be subject to unblinding (as applicable) and regulatory reporting: signs and symptoms of PAH worsening/exacerbation/progression, abdominal pain, anorexia, chest pain, cyanosis, diaphoresis, dizziness, pre-syncope, syncope, dyspnea, orthopnea, fatigue, hemoptysis, heart failure, hypoxia, palpitations, collapse, systemic

arterial hypotension, and tachycardia. Like all other SAEs, these SAEs must be reported on an SAE form by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event, and be reported on the AE page of the eCRF.

10.3 Pregnancy

If a female subject becomes pregnant, the instructions in Section 5.1.11 must be followed. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring after study start (i.e., signing of informed consent) and up to 1 month following discontinuation of the last of the 3 study treatments must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on the AE page in the eCRF.

10.3.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Actelion drug safety department.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.3.1.

10.4 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, vital signs, and project-specific laboratories/examinations as required) is monitored and reviewed on a continuous basis by the Actelion Clinical Team (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical studies activities from protocol conception to database closure. In addition, an IDMC is monitoring safety data [see Section 3.3].

11 STATISTICAL METHODS

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

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

11.1 Analysis sets

11.1.1 Screened Analysis Set

This analysis set includes all subjects who were screened.

11.1.2 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).

11.1.3 Modified Full Analysis Set

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 (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).

11.1.4 Per-protocol Set

The Per-protocol 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. Major protocol deviations will be described in the SAP. Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received).

11.1.5 Safety Set

The Safety Set includes all subjects who received at least one dose of any of the 3 study treatments.

11.1.6 Usage of the analysis sets

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

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

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

11.2 Variables

11.2.1 Primary efficacy variable

The primary efficacy variable is the ratio of Week 26 to baseline PVR. In the analyses this variable will be log-transformed, as log-transformed ratios follow a normal distribution more closely. In addition, the mean change from baseline on log scale can be transformed into a geometric mean ratio (GMR) of Week 26 to baseline PVR. A GMR < 1 corresponds to a reduction in PVR from baseline, which reflects a positive treatment effect.

Baseline is defined as the last measurement obtained before or on Day 1 (before randomization).

11.2.2 Secondary efficacy variables

See Section 6.1.2.

11.2.3 Other efficacy variables

See Section 6.1.3.

11.2.4 Safety variables

See Section 6.2.

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

The analysis of the primary endpoint, i.e., PVR, will be tested according to the sequential group design of this trial. The first look, i.e., the futility interim analysis (non-binding), will be performed at information time 0.33 (i.e., when 33% of the planned enrolled subjects in each arm have completed their Week 26 visit) and the final one at the end of the study (i.e., when all subjects have completed their Week 26 visit). The overall type I error will be preserved at a 5% level.

To control for multiplicity across the primary and selected secondary efficacy endpoints, statistical analyses for secondary endpoints 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.

11.3.2 Analysis of the primary efficacy variable

11.3.2.1 Hypotheses and statistical model

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.

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.

11.3.2.2 Handling of missing data

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 last observation carried forward approach is expected to be conservative.

11.3.2.3 Main analysis

Following the intent-to-treat principle, the primary analysis will be conducted on the FAS.

The same method will be considered for the primary efficacy endpoint at time of interim analysis and at final analysis. The only difference will be the significance level as indicated further below.

The ratio of Week 26 to baseline PVR will be log-transformed (base e) and analyzed using an analysis of covariance (ANCOVA) with factors for treatment group, region (as stratified at randomization), baseline WHO FC (as stratified) and a continuous covariate for baseline log PVR. The treatment group difference (triple minus dual) and its corresponding CI will be estimated based on the model.

For each treatment group, the GMR of Week 26 to baseline PVR will be obtained by exponentiating the least squares means from the model. The triple versus dual treatment group ratio of GMRs and its corresponding CI will be obtained by exponentiating the treatment group difference and its corresponding CI from the model.

The null hypothesis will be rejected if the corresponding CI around the ratio of GMRs excludes 1. Triple therapy will be considered superior to dual therapy if the corresponding CI is entirely below 1.

11.3.2.4 Supportive/sensitivity analyses

Supportive analyses will be performed for the Modified FAS as well as for the PPS. Additional sensitivity analyses will be described in the SAP.

11.3.2.5 Subgroup analyses

Subgroup analyses will be performed by region and WHO FC at baseline (I/II versus III/IV). Additional subgroups analyses will be described in the SAP.

11.3.3 Analysis of the secondary efficacy variables

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.

Change from baseline to Week 26 in NT-proBNP (log-transformed) will be analyzed using an ANCOVA with factors for treatment group, region, baseline WHO FC, and a covariate for baseline NT-proBNP (log-transformed).

Change from baseline to Week 26 in 6MWD will be analyzed using an ANCOVA with the same factors and a continuous covariate for baseline 6MWD.

Absence of worsening from baseline to Week 26 in WHO FC will be analyzed using a logistic regression model with factors for treatment group, region, and baseline WHO FC. Subjects in WHO FC IV at baseline will be excluded from the latter analysis. A sensitivity analysis will be performed including subjects in WHO FC IV at baseline (for whom worsening will be defined as death or hospitalization due to PAH).

Changes from baseline to Week 26 in RHC variables other than PVR will be analyzed using an ANCOVA with factors for treatment group, region, baseline WHO FC, and a continuous covariate for the baseline value of the variable.

Time from randomization to first disease progression event (censored at EOMOP plus 7 days) will be described by Kaplan-Meier plots and analyzed by the logrank test and a Cox model with factors for treatment group, region and baseline WHO FC. These analyses

will also be performed in the subset of subjects from the FAS who received at least one dose of double-blind study treatment. In that case the variable is defined as time from first double-blind study treatment intake to first disease progression event (censored at end of double-blind study treatment plus 7 days, or EOMOP plus 7 days, whichever is first).

The components of the first occurrence of disease progression events will be tabulated by treatment group. If for a given subject two components occur on the same day then the worst will be tabulated (according to the hierarchy: death, hospitalization, initiation of therapy for worsening PAH, and clinical worsening).

Analysis of efficacy variables between EOMOP and EOT (i.e., after the main observation period) will be described in the SAP.

11.3.4 Analysis of the other efficacy variables

Changes from baseline to all regular collection timepoints in NT-proBNP (log-transformed) will be analyzed using a mixed model for repeated measurements with factors for treatment group, visit and treatment by visit interaction and a continuous covariate for baseline NT-proBNP (log-transformed). An unstructured covariance matrix will be used to account for the correlation between measurements of the same subject.

Changes from baseline to all regular visits in 6MWD will be analyzed using the same model, but with a covariate for baseline 6MWD.

Absence of worsening from baseline to all regular visits in WHO FC will be summarized by treatment group using descriptive statistics. Subjects in WHO FC IV at baseline will be excluded from this analysis.

Unsatisfactory clinical response will be summarized by treatment group using descriptive statistics. This analysis will also be performed excluding subjects who already have an unsatisfactory 'response' at baseline (i.e., WHO FC III or IV or a baseline 6MWD $\leq$ 440 m, accompanied by NT-proBNP $\geq 3 \times$ ULN).

The number of treatment goals met at Week 26 (0–5) will be compared between treatment groups using the Cochran-Mantel-Haenszel test, stratified by baseline WHO FC and 6MWD ($\leq$ 440 m versus > 440 m). This analysis will also be performed excluding subjects who already had one or more goals met at baseline.

Analysis of efficacy variables between EOMOP and EOT (i.e., after the main observation period) will be described in the SAP.

11.3.5 Analysis of the safety variables

All safety analyses will be performed on the Safety Set using descriptive statistics. Where indicated, safety analyses will also be performed on the subset of subjects who received at

least one dose of double-blind study treatment (i.e., selexipag or placebo). All safety data will be listed, with flags for quantitative abnormalities. AEs in subjects who were screened but not randomized will be listed. Safety analysis periods are described in Section 6.2.

11.3.5.1 Adverse events

A treatment-emergent AE is any AE temporally associated with the use of any of the 3 study treatments. The number and percentage of subjects experiencing treatment emergent AEs and SAEs at least once will be tabulated by treatment group and by:

- MedDRA system organ class (SOC) and individual preferred term within each SOC, in descending order of incidence.
- Frequency of subjects with events coded with the same preferred term, in descending order of incidence.

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

AEs leading to premature discontinuation of any of the 3 study treatments and AEs with outcome death will be summarized as described above.

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

Additionally, AE and SAE tables will be provided for the subset of subjects who received at least one dose of double-blind study treatment. In these tables only AEs with onset between the first and last day of double-blind study treatment will be included. AEs specifically related to double-blind study treatment will be tabulated as described above. AEs leading to premature discontinuation of double-blind study treatment and AEs on double-blind study treatment with outcome death will be summarized similarly. AEs and SAEs with onset between randomization and first day of double-blind study treatment will also be summarized.

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

11.3.5.2 Laboratory variables

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

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

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

For laboratory variables measured see Section 7.3.7.2.

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

11.3.5.3 Vital signs and body weight

Vital signs, HR, and body weight will be summarized at each study visit using the usual location and scale summary statistics by treatment group for both absolute values and changes from baseline. Subjects for whom no post-baseline value is available are excluded from the analysis of the changes from baseline in the Safety Set.

11.3.6 Analysis of other variable(s)

The individual maintenance dose for selexipag (or placebo) —defined as the dose to which a subject was exposed for the longest duration during the maintenance period— will be summarized using descriptive statistics.

11.4 Interim analyses

A formal interim analysis is planned at information time of 0.33, i.e., when 33% of planned enrolled subjects in each arm have completed their Week 26 visit 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 IDMC will review the efficacy, safety and tolerability data at regular intervals prior to and after the interim analysis.

Access to randomization information will be limited to the independent SAC which will prepare all unblinded outputs for the interim analysis and for the regular IDMC reviews. The SAC will be represented by an independent statistician.

The interim analysis will be formally performed on the primary efficacy endpoint. However, to ensure adequate and sufficient data for the interpretation and decision making, descriptive statistics will also be provided for other efficacy endpoints, selected safety variables (adverse events, selected laboratory abnormalities), exposure, and demographic data.

11.5 Sample size

11.5.1 Sample size justification

Table 3 shows published PVR data from studies of initial dual therapy (bosentan and epoprostenol [Humbert 2004, Kemp 2012, Sitbon 2017]) and initial triple therapy (bosentan, epoprostenol and sildenafil [Sitbon 2014]). In addition, unpublished data from initial dual therapy were included [Sitbon 2015, unpublished].

The four studies of initial dual therapy reported reductions (calculated) of PVR from baseline ranging from 40% to 54% [Sitbon 2017]. The observational study of initial triple therapy reported a reduction (calculated) of PVR of 68% (95% CI: 62%–74%) [Sitbon 2014].

For the anticipated treatment difference (triple versus dual therapy group) it should be noted that the data from Table 3 are from different studies that may not be fully comparable and that the information on initial triple therapy is limited (n = 18). Taking into account those limitations (as well as the possibly less pronounced PVR reduction in subjects that do not complete 26 weeks of treatment) it is anticipated that the reduction in PVR from baseline in the dual therapy group is approximately 50% (GMR = 0.50), whereas the PVR reduction in the triple therapy is approximately 60% (GMR = 0.40), corresponding to a ratio of geometric means of 0.80 (20% difference in favor of triple therapy). This corresponds to a treatment difference on log scale of −0.223 (i.e., log(0.40) –log(0.50)).

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 the published PVR data where SD ranged from 0.38 to 0.44. For this trial, a more conservative SD = 0.5 on the log-scale was assumed.

Considering a one-step analysis, i.e., no interim analysis, to detect a treatment difference of −0.223 with an SD of 0.5 (both on log-scale), a total of 212 subjects (106 per group) would be needed for 90% power (two-sided $\alpha = 0.05$).

However, this trial is considering an early stopping for futility, which impacts the overall number of subjects. Under the same hypothesis, and considering a group sequential design, with a Pocock boundary, and a non-binding interim analysis performed at information time 0.33, the number of subjects needed to demonstrate this difference (i.e., –0.223) at the final analysis is increased to 238 subjects.

The interim analysis is to be performed when 33% of the planned total number of subjects have completed the Week 26 PVR assessment or prematurely discontinued the study. Under those assumptions and considering the current selected boundary, it is expected that the study should be stopped if a reduction compared to placebo (on log scale) lower than or equal to 0.042 is observed (assuming equal SD of 0.5). In other words, H_1 (reduction of approximately 0.223 on a log scale compared to placebo) is to be rejected if a p-value ≥ 0.706 is observed at interim analysis [Table 4].

Table 3 Mean and SD for PVR, log-transformed PVR and change from baseline on log-scale

		N	Mean dyn.s^{-1}cm^{-5}	SD dyn.s^{-1}cm^{-5}	SD (log-scale)	Mean (log-scale)	GMR (% red)[2] [95% CI]
Dual Therapy							
Humbert 2004	Baseline	22	1511	605.1	0.39	7.25	
	Week 16	22	947	487.8	0.49	6.74	
	CFB[1]	22	-	-	**0.44**	**−0.51**	**0.60 (40%)** [27%–50%]
Kemp 2012	Baseline	23	1493	398	0.26	7.27	
	Month 4	23	784	364	0.44	6.57	
	CFB	23	-	-	**0.38**	**−0.71**	**0.49 (51%)** [42%–58%]
Sitbon 2015 (unpublished)	Baseline	52	1076	385	0.35	6.92	
	Month 4	52	620	292	0.45	6.33	
	CFB	52	-	-	**0.41**	**−0.59**	**0.55 (45%)** [38%–51%]
Sitbon 2017	Baseline	16	808	312	**NC**[3]	**NC**[3]	
	Week 16	16	384	184	**NC**[3]	**NC**[3]	
	CFB	16	-	-	**NC**[3]	**NC**[3]	**0.46 (54%)**

		N	Mean dyn.s^{-1}cm^{-5}	SD dyn.s^{-1}cm^{-5}	SD (log-scale)	Mean (log-scale)	GMR (% red)[2] [95% CI]
							[48%–60%]
Triple Therapy							
Sitbon 2014	Baseline	18	1718	627	0.35	7.39	
	Month 4	18	564	260	0.44	6.24	
	CFB	18	-	-	**0.40**	**−1.15**	**0.32 (68%)** [62%–74%]

The means and SDs for untransformed PVR were taken from the publications, whereas the means and SDs for log-transformed PVR were calculated from those.

[1] Change from baseline. For the SD on log scale a correlation of 0.5 was assumed between baseline and post-baseline.

[2] Geometric Mean Ratio to baseline (percentage reduction from baseline).

CFB = change from baseline; CI = confidence interval; GMR = geometric mean ratio; PVR = pulmonary vascular resistance; SD = standard deviation.

[3] NC = "Not Calculated" as treatment effect is directly provided in reference.

11.5.2 Sample size sensitivity

Table 4 shows the sample sizes when the assumptions about PVR reduction from baseline (50% in the dual therapy group versus 60% in the triple therapy group) are not entirely met. For the dual therapy group 40% to 60% reduction was considered and for the triple therapy group an additional 10% to 15% reduction was assumed.

Table 4 Sample sizes needed for 90% power at final analysis, and stopping value for futility at interim analysis (two-sided α = 0.05, SD = 0.5, information time = 0.33)

PVR reduction in dual therapy group	PVR reduction in triple therapy group	Treatment effect GMR (% red)(2)	Number of subjects	Number of subjects at interim analysis	Stop for futility if PVR reduction in triple therapy group ≤ (1)	Stop for futility if p-value ≥
40%	55%	0.75 (25%)	144	48	43.21%	0.704
40%	50%	0.83 (17%)	357	119	42.06%	0.703
50%	65%	0.70 (30%)	91	31	53.19%	0.713
50%	**60%**	**0.80 (20%)**	**238**	**79**	**52.06%**	**0.706**
60%	75%	0.63 (37%)	54	18	63.34%	0.705
60%	70%	0.75 (25%)	144	48	62.21%	0.704

Retained scenario (dual: 50% / triple: 60%) appears in bold. PVR = pulmonary vascular resistance, SD = standard deviation.

(1) Lowest PVR reduction in the triple combination below which, for the corresponding dual therapy PVR reduction, the difference with the dual therapy implies rejection of H1.

(2) Geometric Mean Ratio (GMR) of triple therapy over dual therapy (percentage reduction).

It can be seen that the proposed sample size of 238 subjects is robust to most deviations from the assumptions. Calculations were done using software EAST version 6.4.

12 DATA HANDLING

12.1 Data collection

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

Case Report Form (CRF) data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site staff will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (according to 21 CFR Part 11).

Subject Screening data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason is noted in the eCRF. However, the subject is not obliged to provide a reason.

12.2 Maintenance of data confidentiality

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

12.3 Database management and quality control

Electronic CRFs will be used for all subjects. The investigator/delegate will have access to the site eCRF data until the database is closed. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any timepoint during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of regulatory authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples will be processed through a central laboratory and the results will be loaded electronically into the clinical database [for exceptions see Section 7.3.7.1].

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

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

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

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB or IEC. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

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

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

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason and without having to provide any justification.

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

Site staff authorized to participate to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on Actelion Delegation of Authority form. A study physician must always be involved in the consent process.

The subject and/or legal representative must sign, personally date and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated and timed (if the first study-mandated procedure was performed on the same day informed consent was obtained) by the authorized site staff listed on Actelion Delegation of Authority form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.The informed consent process must be fully documented in the subject's medical records. This must include the study reference, the subject number, the date and, if applicable, time when the subject was first introduced to Actelion clinical study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional person present during the consent process (e.g., subject family member), a copy of the signed ICF given to the subject / legal representative.

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

13.4 Compensation to subjects and investigators

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

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

13.5 Protocol adherence/compliance

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

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

13.6 Protocol amendments

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

13.7 Essential documents and retention of documents

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

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

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

study records to another party, or move them to another location, Actelion must be notified in advance.

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

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

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

13.8 Monitoring

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

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

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

During the study, the monitor will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being

entered in the eCRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

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

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

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

13.9 Investigator Site File

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH E6 GCP Section 8.

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

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

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

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

13.10 Audit

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

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

13.11 Inspections

Regulatory authorities and/or IRB/IEC may also conduct an inspection of Actelion's clinical study (during the study or after its completion).

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

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

13.12 Reporting of study results and publication

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the coordinating investigator (or PI for single-center studies).

The coordinating investigator and the SC, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Actelion will post results from this clinical study on Actelion's Clinical Trial Register and on external/national registries, as required by local law.

Actelion's Policy on Disclosure of Clinical Research Information can be found at:
http://www.actelion.com/documents/corporate/policies-charters/policy-clinical-research-information.pdf

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

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

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

14 REFERENCES

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