Macitentan / ACT-064992

Pulmonary arterial hypertension

Protocol AC-055-403

REPAIR: Right vEntricular remodeling in Pulmonary ArterIal hypeRtension

A prospective, multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on Right vEntricular remodeling in Pulmonary ArterIal hypeRtension assessed by cardiac magnetic resonance imaging

Study Phase:	4
EudraCT Number:	2014-004066-20
Status and version:	Final Version 6
Date:	8 November 2016
Actelion document number (Doc No.):	D-16.554

SPONSOR CONTACT DETAILS

SPONSOR	ACTELION Pharmaceuticals Ltd Gewerbestrasse 16 CH-4123 Allschwil Switzerland
Clinical Trial Physician	Maziar Assadi-Gehr / Global Medical Affairs Physician ☎ [redacted] Fax E-mail

MEDICAL HOTLINE
Toll phone number: [redacted]

Site-specific toll telephone numbers and toll-free numbers for the Medical Hotline can be found in the Investigator Site File.

ACTELION CONTRIBUTORS TO THE PROTOCOL

Clinical Trial Scientist	[redacted] Clinical Scientist
Clinical Trial Statistician	Nicolas Martin, Expert Statistician
Drug Safety Physician	[redacted] Senior Clinical Drug Safety Physician

COORDINATING INVESTIGATOR

Name / Title	**Address**
Nazzareno Galiè, MD	Istituto di Cardiologia, Universita` di Bologna via Massarenti, [redacted] [redacted], Italy

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

CENTRAL LABORATORY	Covance Central Laboratory Services SA [redacted]Switzerland
CENTRAL IMAGE REPOSITORY (Cardiac MRI, RHC curves, PET-MR, Echo)	World Care Clinical (WCC) [redacted]USA
IMAGE ANALYSIS CENTER-cardiac MRI	VUMC [redacted]The Netherlands
CENTRAL ASSESSMENT-PET-MR	MGH Massachusetts General Hospital [redacted]Massachusetts
CENTRAL ASSESSMENT-Echo	World Care Clinical (WCC) [redacted]USA
CRO (MONITORING)	TFS [redacted]Sweden Chiltern International [redacted]UK
HOME PHLEBOTOMY SERVICE	Global Care Clinical Trials Ltd [redacted]USA
BIOSTATISTICS	Datametrix [redacted]Switzerland

A list of site-specific contact details for CROs can be found in the Investigator Site File.

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Macitentan / ACT-064992

Indication

Pulmonary arterial hypertension

Protocol number, study acronym, study title

AC-055-403, REPAIR, A prospective, multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on Right vEntricular remodeling in Pulmonary ArterIal hypeRtension assessed by cardiac magnetic resonance imaging

I approve the design of this study.

TITLE	NAME	DATE	SIGNATURE
Clinical Trial Physician	Maziar Assadi-Gehr	8.11.2016	[redacted]
Clinical Trial Statistician	Nicolas Martin	8.11.2016	[redacted]

INVESTIGATOR SIGNATURE PAGE

Treatment name / number
Macitentan / ACT-064992

Indication
Pulmonary arterial hypertension

Protocol number, study acronym, study title
AC-055-403, REPAIR, A prospective, multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on Right vEntricular remodeling in Pulmonary ArterIal hypeRtension assessed by cardiac magnetic resonance imaging

I agree to the terms and conditions relating to this study as defined in this protocol, 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 patients (other than those procedures necessary for the wellbeing of the patients).

I agree to conduct this study in accordance with 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 patients 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 Health Authorities worldwide.

	Country	Site number	Town	Date	Signature
Site Principal Investigator					

This center participates in:
- ☐ Metabolism sub-study
- ☐ Biopsy sub-study
- ☐ Echo sub-study

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

2D	2-dimensional
3D	3-dimensional
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
CD	Compact Disc
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CIR	Central Image Repository
CL	Confidence limit
CO	Cardiac output
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficients of Variation
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 isozyme 3A4
DL_{CO}	Diffusing capacity of the lung for carbon monoxide
dPAP	Diastolic pulmonary arterial pressure
dSAP	Diastolic systemic arterial pressure
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1
ETA	Endothelin A receptor
ETB	Endothelin B receptor
FAS	Full Analysis Set
FC	Functional Class
FDG	Fluorodeoxyglucose
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice

GDF-15	Growth differentiation factor-15
GMP	Good Manufacturing Practice
HAESI	Hepatic adverse events of special interest
HIV	Human immunodeficiency virus
HR	Heart rate
i.v.	Intravenous
IAC	Image Analysis Center
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Journal Editors
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board
INR	International Normalized Ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigative Site File
IUD	Intrauterine device
IUS	Intrauterine system
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of the normal range
LV	Left Ventricular
LVEDP	Left Ventricular End Diastolic Pressure
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LVSV	Left Ventricular Stroke Volume
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary arterial pressure
MR	Magnetic resonance
mRAP	Mean right atrial pressure
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
NT-proBNP	N-terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PBMC	Peripheral blood mononuclear cell
PCWP	Pulmonary capillary wedge pressure

PDE-5	Phosphodiesterase type-5
PET	Positron Emission Tomography
PH	Pulmonary hypertension
PPS	Per Protocol Set
PT	Preferred term
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RTI	Rescue Therapy Initiation
RV	Right ventricle, right ventricular
RVEDV	Right Ventricular End Diastolic Volume
RVEF	Right Ventricular Ejection Fraction
RVESV	Right Ventricular End Systolic Volume
RVSV	Right Ventricular Stroke Volume
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIV	Site Initiation Visit
SOC	System organ class
SOP	Standard operating procedure
sPAP	Systolic pulmonary arterial pressure
SS	Safety Set
sSAP	Systolic systemic arterial pressure
TAPSE	Tricuspid annular plane systolic excursion
TNF	Tumor Necrosis Factor
ULN	Upper limit of the normal range
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WU	Woods Units

PROTOCOL SYNOPSIS AC-055-403

TITLE	A prospective, multicenter, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on Right vEntricular remodeling in Pulmonary ArterIal hypeRtension assessed by cardiac magnetic resonance imaging.
ACRONYM	REPAIR: **R**ight v**E**ntricular remodeling in **P**ulmonary **A**rter**I**al hype**R**tension
OBJECTIVES	**Primary objective** To evaluate the effect of macitentan on right ventricular and hemodynamic properties in patients with symptomatic pulmonary arterial hypertension (PAH). **Secondary objective** To evaluate the safety and tolerability of macitentan in patients with symptomatic PAH. **Exploratory objectives** To investigate the effect of macitentan on disease-related circulating biomarkers in patients with symptomatic PAH. To explore a potential association between change in right ventricular properties and clinical outcome in patients with symptomatic PAH. To investigate the effect of macitentan on ventriculo-arterial coupling in patients with symptomatic PAH. To evaluate the effect of macitentan on left ventricular (LV) properties in patients with symptomatic PAH.
DESIGN	Prospective, multicenter, single-arm, open-label, Phase 4 study.
PERIODS	**Screening:** from informed consent signature to initiation of study treatment, may last up to 28 days. **Treatment period:** from first dose intake (Day 1) to End of Treatment (EOT) at Week 52 ± 7 days or at premature discontinuation of study treatment. **The Safety follow-up period** lasts at least 30 days and ends with the End of Study (EOS) Visit 30 to 37 days after EOT.

PLANNED DURATION	Approximately 3 years from first patient, first visit to last patient, last visit.
SITE(S) / COUNTRY(IES)	Approximately 50 sites in approximately 12 countries in Asia, Australia, Europe, and North America.
SUBJECTS / GROUPS	100 patients enrolled in one group.
MAIN INCLUSION CRITERIA	1. Signed informed consent prior to any study-mandated procedure. 2. Symptomatic PAH. 3. World Health Organization (WHO) Functional Class (FC) I to III. 4. PAH etiology belonging to one of the following groups according to Nice classification: 1.1 Idiopathic PAH 1.2 Heritable PAH 1.3 Drug- and toxin-induced PAH 1.4.1 PAH associated with connective tissue disease 1.4.4 PAH associated with congenital heart diseases: **only simple** (atrial septal defect, ventricular septal defect, patent ductus arteriosus) **congenital systemic to pulmonary shunts at least 2 year post surgical repair.** 5. Hemodynamic diagnosis of PAH confirmed by right heart catheterization (RHC) performed between Day −28 and Day 1 (inclusion RHC; RHC data obtained at study site within this time frame, prior to obtaining signed informed consent, are acceptable) showing: • Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg *and* – Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 12 mmHg and pulmonary vascular resistance (PVR) ≥ 4 Woods Units (WU) (320 dyn.sec.cm^{-5}) *or* – 12 mmHg ≤ PCWP or LVEDP ≤ 15 mmHg and PVR ≥ 6 WU (480 dyn.sec.cm^{-5}). 6. 6-minute walk distance (6MWD) ≥ 150 m during screening. 7. For patients treated with oral loop diuretics, treatment dose must have been stable at least 1 month prior to the inclusion RHC.

	8. For patients treated with phosphodiesterase type-5 (PDE-5) inhibitors, treatment dose must have been stable at least 3 months prior to the inclusion RHC (initiation of PDE-5 inhibitors during screening is allowed after all screening assessments have been performed). 9. For patients treated with beta blockers, treatment dose must have been stable at least 1 month prior to the inclusion RHC. 10. Men or women ≥ 18 and < 75 years. For patients aged ≥ 65 and < 75 years, an eligibility form will be submitted to a Steering Committee member who will reserve the right to exclude the patient. 11. Women of childbearing potential [see Section 4.5.1] must: a. Have a negative serum pregnancy test during screening and a negative urine pregnancy test on Day 1, *and* b. Agree to use reliable methods of contraception [see Section 4.5] from screening up to 30 days after study treatment discontinuation, *and* c. Agree to perform monthly pregnancy tests up to 30 days after study treatment discontinuation.
MAIN EXCLUSION CRITERIA	1. Body weight < 40 kg. 2. Body mass index (BMI) > 35kg/m^2. For patients with 30kg/m^2 < BMI < 35kg/m^2, an eligibility form will be submitted to a Steering Committee member who will reserve the right to exclude the patient. 3. Pregnancy, breastfeeding, or intention to become pregnant during the study. 4. Recently started (< 8 weeks prior to informed consent signature) or planned cardio-pulmonary rehabilitation program. 5. Known concomitant life-threatening disease with a life expectancy < 12 months. 6. Any condition likely to affect protocol or treatment compliance. 7. Hospitalization for PAH (except for diagnosis of PAH) within 3 months prior to informed consent signature. 8. Left atrial volume indexed for body surface area (BSA) ≥ 43mL/m^2 by echocardiography or cardiac MRI.

	9. Moderate to severe left-heart valvular disease. 10. History of pulmonary embolism or deep vein thrombosis. 11. 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 (eligible only if no or mild interstitial lung disease on computed tomography). – Forced vital capacity (FVC) < 60% of predicted. – Forced expiratory volume in one second (FEV_1) < 60% of predicted. 12. Moderate to severe restrictive lung disease (i.e., total lung capacity < 60% of predicted value) at any time prior to enrollment. 13. Historical evidence of significant coronary artery disease established by: – History of myocardial infarction *or* – More than 50% stenosis in a coronary artery (by percutaneous coronary intervention or angiography) *or* – Elevation of the ST segment on electrocardiogram *or* – History of coronary artery bypass grafting *or* – Stable angina. 14. Known uncontrolled diabetes mellitus (in the opinion of the investigator). 15. Severe renal insufficiency (calculated creatinine clearance < 30 mL/min). 16. Cancer. 17. Systolic blood pressure < 90 mmHg. 18. 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 an aspartate aminotransferase (AST) elevation > ULN at screening. 19. Hemoglobin < 100g/L. 20. Serum AST and/or alanine aminotransferase (ALT) > 3 × ULN.

	21. Need for dialysis. 22. Responders to acute vasoreactivity test based on medical history. 23. Prior use of endothelin receptor antagonists (ERAs), stimulators of soluble guanylate cyclase or prostacyclin or prostacyclin analogs. 24. Treatment with strong inducers of cytochrome P450 isozyme 3A4 (CYP3A4) within 4 weeks prior to study treatment initiation (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort). 25. Treatment with strong inhibitors of CYP3A4 within 4 weeks prior to study treatment initiation (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir). 26. Treatment with another investigational drug (planned, or taken within the 3 months prior to study treatment initiation). 27. Hypersensitivity to any ERA or any excipients of the formulation of macitentan (lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, polyvinyl alcohol, polysorbate, titanium dioxide, talc, xanthan gum, and lecithin soya). 28. Claustrophobia. 29. MRI-incompatible permanent cardiac pacemaker, automatic internal cardioverter. 30. Metallic implant (e.g., defibrillator, neurostimulator, hearing aid, permanent use of infusion device). 31. Atrial fibrillation, multiple premature ventricular or atrial contractions, or any other condition that would interfere with proper cardiac gating during MRI. 32. **For patients enrolling in the metabolism sub-study only:** glucose intolerance. 33. **For patients enrolling in the biopsy sub-study only:** PAH etiology belonging to Nice classification 1.4.4: PAH associated with congenital heart diseases or 1.4.1: PAH associated with connective tissue disease.

STUDY TREATMENTS	**Investigational treatment** Open-label macitentan 10 mg once daily, oral. **Comparator and/or placebo** Not applicable.
CONCOMITANT THERAPY	**Allowed concomitant therapy until Week 26 RHC** • Therapies allowed at baseline based on eligibility criteria. • Oral loop diuretics if used at a stable dose for 1 week prior to Week 26 RHC. • Use of rescue therapy (see below) only in case of disease progression. • A PDE-5 inhibitor may be initiated from the time when all screening assessments have been performed until Day 14, provided that dose optimization is complete at the latest 14 days after study treatment initiation. **Allowed concomitant therapy after Week 26 RHC** Treatment initiation and dose changes for: • Loop diuretics. • PDE-5 inhibitors. • Prostanoid analogs by any route of administration. • Stimulators of soluble guanylate cyclase. • Any other PAH-specific therapy that may obtain marketing authorization during study conduct. **Forbidden concomitant therapy** ERAs other than study drug, investigational drug other than study drug, strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) and strong inducers of CYP3A4 (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort). Initiation of one of these forbidden medications will lead to premature discontinuation of study treatment. **Rescue therapy before Week 26 RHC** The following treatment changes are allowed before Week 26 RHC only in case of disease progression:

	• Initiation of: – Intravenous (i.v.) loop diuretics – PDE-5 inhibitors – Prostanoid analogs by any route of administration – Stimulators of soluble guanylate cyclase – Any other PAH-specific therapy that may obtain marketing authorization during study conduct. • Up-titration of PDE-5 inhibitors. Disease progression is defined as: • Decrease in 6MWD by more than 15% associated with worsening in WHO FC, *or* • Need for subcutaneous (s.c.) or i.v. prostanoid therapy, *or* • Hospitalization for PAH (investigator's assessment). After Week 26 RHC, treatment changes are allowed.
ENDPOINTS	**Primary efficacy endpoints** The study has two primary efficacy endpoints: - Change from baseline to Week 26 in Right Ventricular (RV) Stroke Volume (RVSV) assessed by cardiac MRI from pulmonary artery flow. - Ratio of Week 26 to baseline PVR assessed by RHC. **Secondary efficacy endpoints** Change from baseline to Week 26 in: - RV End Diastolic Volume (RVEDV) - RV End Systolic Volume (RVESV) - RV Ejection Fraction (RVEF) - RV mass - 6MWD - WHO FC **Exploratory endpoints** Change from baseline to Week 26 in: - mPAP - Mean right atrial pressure - Cardiac index - Arterial elastance - RV end-systolic elastance - RV maximum isovolumic pressure

	Change from baseline to Week 52 in: - RVSV determined by cardiac MRI from pulmonary artery flow - RVEDV - RVESV - RVEF - RV mass - 6MWD - WHO FC Change from baseline to Week 26 and Week 52 in: - Left Ventricular Stroke Volume (LVSV) determined by cardiac MRI from the aortic flow - LV End Diastolic Volume (LVEDV) - LV End Systolic Volume (LVESV) - LV Ejection Fraction (LVEF) - LV mass - RVEDV/LVEDV - RVESV/LVESV - N-terminal pro-brain natriuretic peptide (NT-proBNP) - Uric acid - Red cell distribution width - Activin A - Cystatin C - Follistatin - Galectin-3 - Growth Differentiation Factor (GDF)-15 - Cardiac troponin T - Lactate dehydrogenase (LDH) - Osteoprotegerin - Tumor Necrosis Factor (TNF) alpha Time to first clinical worsening event defined as: - Decrease in 6MWD by > 15% from baseline associated with worsening in WHO FC, *or* - Initiation of s.c. or i.v. prostanoid therapy, *or* - Hospitalization for PAH (investigator's assessment), *or* - Death

	Safety endpoints - Treatment-emergent adverse events (AEs) up to 30 days after EOT. - Treatment-emergent serious adverse events (SAEs) up to 30 days after EOT. - AEs leading to premature discontinuation of study drug - Treatment-emergent marked laboratory abnormalities up to 30 days after EOT. - Occurrence of liver function test (ALT and/or AST) abnormality (≥ 3; ≥ 3 and $< 5 \times$ ULN; ≥ 5 and $< 8 \times$ ULN; $\geq 8 \times$ ULN) up to EOT. - Occurrence of hemoglobin abnormality (≤ 80 g/L; > 80 and ≤ 100 g/L) up to EOT. - Occurrence of ALT and/or AST abnormality $\geq 3 \times$ ULN associated with bilirubin $\geq 2 \times$ ULN.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	• **Analysis sets** The Full Analysis Set (FAS) includes all patients who received at least one dose of study drug and who had a baseline as well as a post-baseline measurement for both primary endpoints (RVSV and PVR). The Modified FAS comprises all patients from the FAS who had a post-baseline measurement taken between 16 and 30 weeks of treatment. The Safety Set (SS) includes all patients who received at least one dose of study drug. • **Primary efficacy endpoints** The study has two primary efficacy endpoints: • Change from baseline to Week 26 in RVSV assessed by cardiac MRI from pulmonary artery flow. • Ratio of Week 26 to baseline PVR assessed by RHC. • **Null and alternative hypotheses** The null hypothesis is: The mean change from baseline in RVSV is less than or equal to zero AND the geometric mean ratio of Week 26 to baseline PVR is greater than or equal to one.

	The alternative hypothesis is: The mean change from baseline in RVSV is greater than zero OR the geometric mean ratio of Week 26 to baseline PVR is less than one. • **Type-I and -II errors and power** The overall type I error (α) of 0.025 (one-sided) will be split between the endpoints: change from baseline in RVSV will be tested at $\alpha = 0.02$ and ratio to baseline PVR will be tested at $\alpha = 0.005$. Per endpoint the type II error is set to 0.10 and the power to 90%. • **Primary efficacy analysis** The primary efficacy analyses (interim and final) will be performed on the Modified FAS. Change from baseline in RVSV will be analyzed using an Analysis of Covariance (ANCOVA) with a factor for other PAH-specific therapy (none, background or initiated at baseline) and a covariate for baseline RVSV. The mean change from baseline and its **96%** confidence interval (CI) will be estimated based on the model. The ratio of Week 26 to baseline PVR will be log transformed (base e) and analyzed using an ANCOVA with a factor for other PAH-specific therapy (none, background or initiated at baseline) and a covariate for baseline log PVR. The mean change from baseline (on log scale) and its **99%** CI will be estimated based on the model. The Geometric Mean Ratio (versus baseline) and its 99% CI will be obtained by exponentiation. If a patient discontinues treatment prematurely before Week 26 or initiates rescue therapy before Week 26, RVSV and PVR obtained at study treatment discontinuation will be carried forward, provided that these measurements were taken after at least 16 weeks of study treatment. The null hypothesis will be tested at interim and final analysis, if study continues, and may be rejected based on pre-defined boundaries.

	• **Secondary analyses** Secondary efficacy variables will be analyzed for the Modified FAS only at final analysis at $\alpha = 0.025$ (one-sided) using 95% CIs. No correction for multiple testing will be applied for these analyses. Association between (change from baseline to Week 26 in) cardiac MRI variables and time to first clinical worsening event will be explored using Cox models. • **Safety endpoints** Safety data will be summarized using descriptive statistics. Safety analyses will be performed on the SS. • **Interim analysis** An interim analysis will be conducted when 42 patients have available assessments data for both primary endpoints. To declare the study positive at the interim analysis, both endpoints must be met. • **Sample size calculation** For MRI-based RVSV, no individual patient data are available at Actelion. Individual RVSV was approximated in the hemodynamic sub-study of SERAPHIN (AC-055-302) combining the cardiac index obtained from the RHC with BSA and heart rate from vital signs measurements. The change from baseline in approximate RVSV was around 9 mL, in line with literature suggesting that a difference of 8–12 mL is clinically relevant [Van Wolferen 2011]. Assuming a standard deviation of 18–22 mL, also based on the hemodynamic sub-study of SERAPHIN, the sample size for 90% power is 30–93 evaluable patients for final analysis ($\alpha = 0.02$, one-sided). The number of patients and efficacy boundaries for the interim analysis are described in Table 3. For PVR, an integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), and the hemodynamic sub-study of SERAPHIN suggested that the mean change from baseline is expected to be around −0.24 on log scale (95% CI: −0.29, −0.19) and that the within group standard deviation is around 0.41 on log scale (90% CI: 0.39, 0.43). Under these assumptions, 30–84 evaluable patients are needed for final analysis for 90% power ($\alpha = 0.005$, one-sided).

	The number of patients and efficacy boundaries for the interim analysis are described in Table 4. To account for patient dropout and non-evaluable images, the sample size was set at 100 patients for the final analysis.
STUDY COMMITTEES	A Steering Committee is involved in the design of the study, will provide guidance on study conduct and interpretation of results, and will support study publications. The committee is governed by a Steering Committee charter. An Image Analysis Center will centrally assess all cardiac MRI results and all pressure-volume results. Assessments will be performed according to a dedicated charter. All variables that are specific to the metabolism sub-study will be centrally assessed. Assessments will be performed according to a dedicated charter. All Echo results will be centrally assessed. Assessments will be performed according to a dedicated charter. An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) provides ongoing assessment and advice regarding serious hepatic adverse events of special interest (HAESI) that require further evaluation during the study as per ILSDRB charter.
SUB-STUDIES	Three sub-studies are planned and described under the same protocol. The sub-studies will be conducted in selected centers. In these centers, all patients eligible for the main study will be offered to participate in the sub-study(ies). **Metabolism sub-study, in the US only** Patients: From 10 to 30 patients eligible for the main study and not matching the additional exclusion criterion number 32: glucose intolerance. Objectives: To assess the effect of macitentan on cardiac and arterial metabolism in patients with symptomatic PAH by Positron Emission Tomography (PET)-Magnetic Resonance (MR) imaging.

	Exploratory endpoints: Change from baseline to Week 26 and to Week 52 in: - RV 18F-fluorodeoxyglucose (FDG) uptake - Aortic 18F-FDG uptake - Right common carotid 18F-FDG uptake - Left common carotid 18F-FDG uptake **Biopsy sub-study** Patients: From 10 to 20 patients eligible for the main study and not matching the additional exclusion criterion number 33: PAH etiology belonging to Nice classification 1.4.4: PAH associated with congenital heart diseases or 1.4.1: PAH associated with connective tissue disease. Objectives: To assess the histological and biochemical effects of macitentan on the endomyocardium of the interventricular septum in patients with symptomatic PAH. To assess the biochemical effects of macitentan on peripheral blood mononuclear cells (PBMC) in patients with symptomatic PAH. Exploratory endpoints: Change from baseline to Week 26 in: - Qualitative assessment of endomyocardium function markers in biopsies - Relative quantitative assessment of endomyocardium function markers in biopsies - Number of capillaries per cardiomyocyte - Mean cardiomyocyte volume - Qualitative assessment of cardiomyocytes - mRNA transcript analysis - PBMC mRNA transcript analysis **Echo sub-study** Patients: From 40 to 50 patients eligible for the main study. Objective: To assess the effect of macitentan on right and left ventricular function by echocardiography in patients with symptomatic PAH. Exploratory endpoints: Change from baseline to Week 26 and Week 52 in: - LV eccentricity index at end-diastole

	- LV eccentricity index at end-systole - Minimum diameter of the inferior vena cava (at inspiration) - Maximum diameter of the inferior vena cava (at end-expiration) - Tricuspid annular plane systolic excursion (TAPSE) - Pericardial effusion size scored from 0 to 4 - RV acceleration time, by tissue Doppler and pulsed wave Doppler - RV ejection time, by tissue Doppler and pulsed wave Doppler - Total RV Systolic Time (duration of tricuspid insufficiency jet) - Doppler RV index (RV myocardial performance index), by tissue Doppler and pulsed wave Doppler - Tricuspid peak jet velocity - RV systolic pressure (estimated by tricuspid valve Doppler) - Early diastolic velocity of the jet of pulmonary valve regurgitation - End-diastolic velocity of the jet of pulmonary valve regurgitation - Cardiac output determined from LV outflow tract - Mitral E-wave velocity - Mitral A-wave velocity - Mitral annulus peak early diastolic velocity E' - E/A ratio - E/E' ratio - 2-dimensional (2D) RV dimension end-diastole - Tricuspid peak annular velocity s' - RV end diastolic area - RV end systolic area - RV fractional area change - RVSV determined from pulmonary valve Doppler and pulmonary annulus dimension - Tricuspid peak E, peak A, deceleration time - Tricuspid peak diastolic annular velocities e', a' - LVEDV determined from 2D measurements - LVESV determined from 2D measurements - Mitral deceleration time

	- Mitral annular plane tissue Doppler velocity a' - 2D Global Longitudinal RV strain - 2D circumferential RV strain - Time to peak RV strain - RVSV - RVEDV - RVESV - RVEF - RV mass - LVSV - LVEDV - LVESV - LVEF - LV mass - RVEDV/LVEDV - RVESV/LVESV

Table 1 Visit and assessment schedule

PERIODS	SCREENING	TREATMENT							FOLLOW-UP
Duration	*Up to 28 days*	*52 weeks*							*Up to 37 days*
VISITS name	*Screening*	*Treatment initiation*	*RTI visit*	*Premature EOT visit (if before Week 26 RHC)*	*Week 26 visit*	*Premature EOT visit (if after Week 26 RHC)*	*EOT visit*[1]	*Unscheduled visit*	*EOS visit (phone)*
Time	*Day −28 to Day 1*	*Day 1*	*Prior to initiation of rescue therapy*	*Prem. EOT: latest 7 days after decision to end study treatment*	*Week 26 (± 14 days)*	*Latest 7 days after decision to end study treatment*	*Week 52 (± 7 days)*		*30 to 37 days after EOT*
Informed consent	X								
Eligibility criteria	X								
Demographic & baseline characteristics	X								
Medical history	X								
Weight	X		X	X	X	X	X	X [10]	
Medications	X	X	X	X	X	X	X	X	X
Birth control methods[7]	X	X	X	X	X	X	X	X	X
Physical exam and vital signs	X	X	X	X	X	X	X	X [10]	
6MWT and Borg	X		X	X	X	X	X	X [10]	
WHO FC	X		X	X	X	X	X	X [10]	
Cardiac MRI	X [2]		X [2,3,4]	X [2,3,4]	X [2]	X [6]	X		
RHC	X [2, 11]		X [2,3,4]	X [2,3,4]	X [2]				
Laboratory tests incl. storage [5]	X		X	X	X	X	X		
Liver and hemoglobin tests	X	Monthly during the first 6 months				Recommended monthly			
Pregnancy test[7,8]		X	Monthly				X		X
PET-MR scan	X [9]		X [4,9]	X [4,9]	X [9]	X [9]	X [9]		
Biopsy	X [9]		X [3,4,9]	X [3,4,9]	X [9]				
Echo	X [9]		X [4,9]	X [4,9]	X [9]	X [9]	X [9]		
Study drug dispensing/return		X		X	X	X	X		
AEs and SAEs	X	X	X	X	X	X	X	X	X

6MWT, six-minute walk test; AE, adverse event; EOS, end of study; EOT, end of treatment; MRI, magnetic resonance imaging; PET-MR, positron emission tomography- magnetic resonance; Prem., premature; RHC, right heart catheterization; RTI, rescue therapy initiation; SAE, serious AE; WHO FC, World Health Organization functional class. 1. Not performed for patients who had a premature EOT previously; 2. Cardiac MRI and RHC must be performed within 21 days of each other; 3. If visit is before Week 16, decision to conduct the exam based on clinical judgment; 4. Done once only and replaces Week 26 exam; 5.Stored samples will be destroyed 1 year after the last patient's last visit; 6.If visit is before Week 48, decision to conduct the exam based on clinical judgment; 7. For women of childbearing potential only; 8. Pregnancy tests will be done using the monthly blood draws where applicable, and with urine pregnancy tests otherwise; 9. For patients in the respective sub-study only; 10. Assessed if clinically indicated; 11. RHC data obtained at study site between Day −28 and Day 1, prior to obtaining signed informed consent, are acceptable.

PROTOCOL

1 BACKGROUND

1.1 Indication

1.1.1 Pulmonary arterial hypertension

The most serious chronic disorder of the pulmonary circulation is pulmonary arterial hypertension (PAH), a syndrome of diverse etiology and pathogenesis characterized by a progressive increase in pulmonary arterial pressure (PAP) and in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death [Benza 2010, Kylhammar 2014, Oudiz 2013].

PAH is associated with structural changes in both pulmonary vasculature and right ventricle. The changes in vascular structure involve three combined elements: vasoconstriction, vascular-wall remodeling, and thrombosis in situ [Humbert 2004]. The changes in the right ventricle mainly consist of hypertrophy, dilation, altered contractility and septal bowing [Rich 2012, Franco 2012, Vonk-Noordegraaf 2011]. Collectively these changes of the right ventricle are termed remodeling.

PAH is hemodynamically defined as a resting mean pulmonary arterial pressure (mPAP) greater than 25 mmHg with normal pulmonary capillary or left atrial pressure (< 15 mmHg) and a PVR greater than 3 Woods 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 drugs and toxins, or it can be associated with a connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.

1.1.2 Treatments

Currently, there is no cure for PAH. However, recent advances in the understanding of the pathogenic factors leading to the pulmonary vascular disease have led to the development of new therapies targeting specific pathways (prostacyclin pathway, endothelin pathway, and nitric oxide pathway) [Galiè 2013] that are believed to play important pathogenic roles.

Several agents are currently approved for the treatment of PAH in the United States, Europe, and Australia. Intravenous (i.v.) prostacyclin (epoprostenol), prostanoid analogs, i.e., treprostinil (i.v., subcutaneous [s.c.], inhaled and oral), and iloprost (i.v. and inhaled),

dual endothelin receptor antagonists (ERAs; bosentan and macitentan), a selective ERA (ambrisentan), phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil and tadalafil), and more recently, a stimulator of soluble guanylate cyclase (riociguat).

Vasodilators, such as calcium channel blockers, are effective only in a minority of patients who have an acute response to vasodilator testing [Rich 1992, Sitbon 2005].

Despite these achievements, PAH remains a serious life-threatening condition [Galiè 2013, Benza 2010], and new compounds continue to be explored.

1.2 Study treatment

1.2.1 Endothelin pathway

Endothelin-1 (ET-1), a 21 amino acid-peptide, is one of the most potent vasoconstrictors and mitogens for smooth muscle, and contributes to increased vascular tone and proliferation in pulmonary vasculopathy [Galiè 2004].

There are two distinct receptors for ET-1, endothelin receptor A (ETA) and endothelin receptor B (ETB). Each receptor has unique binding location and affinity for the endothelin peptide [Benigni 1995, Massaki 1998]. ETA receptors are expressed on pulmonary vascular smooth muscle cells, whereas ETB receptors are present both on pulmonary vascular cells and on smooth muscle cells.

When activated, ETA receptors located in pulmonary vascular smooth muscle cells mediate a potent vasoconstrictive response and ETB receptors on endothelial cells mediate vasodilatation via increased production of nitric oxide and prostacyclin [Hirata 1993, de Nucci 1988]. ET-1 is also known to be a potent mitogen, with the ability to induce cell proliferation in vascular smooth muscle cells. It has been shown that both the ETA and ETB mediate the mitogenic action of ET-1 [Clarke 1989, Chua 1992, Davie 2002, Sugawara 1996].

Laboratory and clinical investigations have shown that ET-1 is overexpressed in several forms of pulmonary vascular disease. ET-1 is likely a major player in the vasodilator and vasoconstrictor imbalance, as well as in the abnormal pulmonary vascular remodeling present in the development and progression of PH of various etiologies [Stewart 1991, Giaid 1993].

1.2.2 Macitentan

Macitentan is approved for the treatment of PAH in the US, EU, Australia, Canada, Japan, Switzerland, New Zealand, Mexico, Israel, Kuwait, South Korea, Argentina, Chile, Singapore, Taiwan, Turkey, Russia, Columbia, Morocco, and Hong Kong.

1.2.2.1 Nonclinical results

Macitentan is an orally active, non-peptide, potent dual ETA and ETB receptor 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 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 found 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.

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

1.2.2.2 Phase 1 results

During the Phase 1 program, more than 200 healthy subjects and about 30 patients (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.

More detailed information on macitentan can be found in the IB [Macitentan IB].

1.2.2.3 Phase 2 results

Phase 2 studies were conducted in patients with mild-to-moderate essential hypertension, and in patients with idiopathic pulmonary fibrosis (IPF). In both indications, macitentan was well tolerated across all dose levels, ranging from 0.3 mg to 10 mg.

A Phase 2 dose-finding study [Macitentan IB] was conducted in patients with mild-to-moderate essential hypertension. In this study, treatment with the 10 mg dose of macitentan was associated with a statistically significant reduction (versus placebo) from baseline to Week 8 in mean sitting diastolic blood pressure at trough, which was the primary endpoint of the study. Macitentan was well tolerated with an overall frequency of AEs similar to that observed in the placebo group. The numbers of patients with at least one serious adverse event (SAE) were evenly distributed across active treatment groups. There were no deaths.

In a Phase 2 study in patients with IPF [Raghu 2013], the primary endpoint (change in forced vital capacity [FVC]) was not met, but it was shown that macitentan treatment with 10 mg dose was well tolerated. Overall, the safety profile was similar in the macitentan 10 mg and placebo groups. The incidence of treatment-emergent AEs was similar in both groups.

More detailed information on macitentan can be found in the IB [Macitentan IB].

1.2.2.4 Phase 3 efficacy results

Effectiveness 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 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 0.547, 97.5% confidence limits (CLs) 0.392–0.762, $p < 0.0001$. This represents a risk reduction of 45%.

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 versus placebo.

A hemodynamic sub-study showed a reduction of PVR from baseline to Month 6 of 36.5%, CLs 21.7–49.2) with macitentan 10 mg.

More detailed information on macitentan can be found in the IB [Macitentan IB].

1.2.2.5 Summary of potential risks and risk management

Nonclinical studies with macitentan did not identify important risks of likely relevance to humans except for teratogenicity, a class effect of ERAs. The protocol, therefore, includes stringent requirements for pregnancy testing and reliable methods of contraception for female patients of childbearing potential.

In the 3 placebo-controlled studies with macitentan, no significant imbalance in liver test elevations was observed across macitentan treatment groups and placebo. The proportions of patients with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations > 3 × upper limit of the normal range (ULN) were similar across the treatment groups, but a higher percentage of patients treated with macitentan 10 mg had ALT > 3 × ULN compared to placebo. However, there were no patients in the studies who met the Hy's Law criteria (i.e., ALT/AST > 3 × ULN and total bilirubin > 2 × ULN), and who had no associated increase in alkaline phosphatase in the absence of alternative explanations which were possibly or likely the cause of the elevations. Patients with serum AST and/or ALT > 3 × ULN are excluded from the study, and monthly liver tests are mandatory during the first 6 months and recommended thereafter. The protocol also includes clear instructions regarding re-tests and criteria for treatment discontinuation in the case of clinically relevant elevations of aminotransferases.

Treatment with ERAs has been associated with increased incidence of edema, anemia and/or decreased hemoglobin [Abman 2009, O'Callaghan 2011]. Treatment with macitentan was associated with a dose-related reduction in hemoglobin levels, which was established within the first 3 months of treatment. Decreased hemoglobin levels tended to show recovery towards baseline after discontinuation of treatment. Higher incidences of anemia AEs were reported in a dose-related fashion in the patients treated with macitentan in comparison to those treated with placebo. Anemia required transfusion in some patients treated with macitentan. Patients with hemoglobin < 100 g/L are excluded from the study. Monthly hemoglobin tests are mandatory during the first 6 months and recommended thereafter. The protocol also includes clear instructions regarding re-tests and criteria for treatment discontinuation in the case of clinically relevant anemia.

The incidences of edema AEs were similar in the macitentan and placebo groups, although subgroup analyses indicated fluctuations in the incidence of edema, with no clear pattern according to treatment (macitentan versus placebo) or macitentan dose. Edema SAEs were uncommon with macitentan treatment and only 3 patients (2 on placebo and 1 on macitentan 10 mg) discontinued treatment due to an edema AE. Overall, there is no indication that edema represents a significant safety concern with macitentan therapy in PAH.

Due to the vasodilatory effects of macitentan, effects on blood pressure might occur. In patients with normal blood pressure prior to initiation of macitentan treatment, there was a slightly higher incidence of AEs denoting hypotension, relative to placebo on macitentan. However, hypotension SAEs were reported less frequently on macitentan than on placebo, and only one macitentan-treated patient discontinued due to this AE. Hypotension AEs were predominantly reported for female patients and there was no indication of an increased incidence in other potentially vulnerable subgroups, such as the elderly, or patients with renal function impairment at baseline. Patients with systolic blood pressure < 90 mmHg are excluded from the study.

Reductions from baseline in leukocyte and platelet counts may be observed with macitentan. In the AC-055-302 / SERAPHIN study, macitentan was associated with modest and non-dose-dependent decreases in mean leukocyte count from baseline to End of Treatment (EOT). A small proportion of PAH patients, in both placebo and macitentan groups, showed markedly reduced platelet counts, with or without bleeding complications, at some time during the study. Resolution during continued treatment with macitentan was observed, as well as absence of recurrence after treatment re-initiation, findings that make a specific, causal relationship to macitentan unlikely.

In the AC-055-302 / SERAPHIN study, menstrual disorder AEs (mainly menorrhagia, metrorrhagia, and dysfunctional bleed) and ovarian cysts were reported at a low incidence overall, but more frequently on macitentan than placebo, in females of

childbearing potential. None of the events led to discontinuation of study drug, there was no consistent drug-dose or drug-exposure pattern, and resolution of menstrual disorder during ongoing treatment was reported in the majority of cases. Confounding factors were present in the majority of these cases. A causal relationship to macitentan remains uncertain.

In clinical trials, a higher reporting rate of upper respiratory tract infections but also bronchitis was seen with macitentan versus placebo. It is likely that many such events may represent symptoms of congestion due to local vasodilatation (e.g., rhinitis), rather than actual infection. For the clinically more relevant lower respiratory tract infections, specially pneumonia, there was no relevant difference between macitentan and placebo. In addition, there was a higher incidence of urinary tract infections and gastroenteritis in the patients who received macitentan treatment compared to those who received placebo. However, given that there was no imbalance in the incidence of these events that were reported as SAEs or that led to discontinuation of treatment, coupled with the fact that there was no increase in the reporting rate over time, these AEs were considered to be of limited clinical relevance.

Given the extensive and long-term controlled data available with macitentan in PAH and the careful follow-up of patients mandated by the protocol, the benefit/risk assessment supports the use of macitentan in the current study.

1.3 Purpose and rationale of the study

1.3.1 Purpose of the study

The purpose of the study is to further extend the knowledge of macitentan by assessing the effects of macitentan on the cardiac muscle, and specifically on the right ventricle.

1.3.2 Rationale

1.3.2.1 Importance of the right ventricle in PAH

The pathophysiologic mechanisms of PAH are initiated by progressive obstructive changes of the pulmonary vasculature which result in increased afterload of the right ventricle. The right ventricle responds by remodeling with increased contractility. Progressively, this increased contractility is no longer sufficient to maintain an appropriate blood supply, the right ventricle hypertrophies, which translates into a thicker myocardium. Dilation is then achieved to increase the blood volume in the right ventricle. Gradually, the right ventricle becomes more spherical so that the septum between right and left ventricles flattens. Right ventricular remodeling compensates for a variable period of time but ultimately may no longer suffice, leading to right heart failure and death.

Although PAH is a disease of the pulmonary vasculature, the geometry and function of the right ventricle are tightly linked with survival [Van Wolferen 2007, Yamada 2012, Swift 2014, Raymond 2002, Van de Veerdonk 2011]. In fact, the primary cause of death in PAH is right ventricular failure. The function of the right ventricle is, therefore, of critical importance in this condition.

While the safety and efficacy of macitentan have been studied in PAH clinical trials, its effects on the right ventricle are yet to be determined.

The capacity of the right ventricle to undergo reverse remodeling has been described in PAH patients who underwent lung transplant [Kasimir 2004], and in patients with PAH treated with single [Wilkins 2005, Galiè 2003, Van Wolferen 2006, Hinderliter 1997, Roeleveld 2004, Blalock 2010] or combined PAH-targeted therapies [Peacock 2014]. It therefore seems reasonable to hypothesize that macitentan reverses right ventricular remodeling.

1.3.2.2 Pulmonary vascular resistance

PAH is characterized by an increased resistance to blood flow in the pulmonary vasculature, quantified by PVR. PVR represents the resistance against which the right ventricle needs to pump. In PAH, a decrease in PVR is therefore beneficial for the right ventricle.

PVR is determined by right heart catheterization (RHC). Since this procedure is indispensable for the diagnosis of PAH and to evaluate treatment response [Galiè 2013], sites treating PAH patients are well experienced with RHC. The study will be run in sites specialized in PAH. RHC procedures in patients with PH in experienced centers are reported to be associated with low morbidity and mortality rates [Hoeper 2006] and deemed acceptable in this study.

1.3.2.3 Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (cardiac MRI) is a safe imaging technique as it is non-invasive and does not use ionizing radiations. Images of slices in any plane can be obtained with very good spatial and temporal resolution. This translates into a low variability of inter-study and inter-rater cardiac MRI assessments which allows a reduced sample size for clinical trials compared to other imaging tools [Addetia 2014].

Cardiac MRI is, therefore, the method of choice to study the evolution of the right ventricle under treatment.

1.3.2.4 Ventriculo-arterial coupling

Beyond the measurement of volumes, a more comprehensive understanding of the balance between right ventricle and the arterial system can be achieved by considering

ventriculo-arterial coupling, which is quantified by the ratio of ventricular end-systolic elastance to arterial elastance [Foëx 1994]. Ventricular end-systolic elastance represents the intrinsic, load-independent contractility of the ventricle. Likewise, arterial elastance represents the load from the pulmonary vasculature that the right ventricle faces.

Elastances are determined from the relationship between volume and pressure in the ventricle. While volume can be measured by cardiac MRI [Trip 2013], the determination of pressure requires RHC [Sunagawa 1980, Takeuchi 1991, Kuehne 2004, Brimioulle 2003]. Determination of ventriculo-arterial coupling does not require any additional procedure for the patient beside cardiac MRI and RHC, which are part of the study.

1.3.2.5 Up-front combination therapy

Based on recent data [Galiè 2014], targeting more than one disease pathway from initial diagnosis may be beneficial.

Thus, combination of a PDE-5 inhibitor and an ERA in a treatment-naïve patient is allowed.

1.3.2.6 Overall benefit-risk ratio

Given the data available with macitentan in PAH, the careful follow-up of patients mandated by the protocol and the acceptable risks of the study procedures, the benefit/risk assessment supports the conduct of the current study.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to evaluate the effect of macitentan on right ventricular and hemodynamic properties in patients with symptomatic PAH.

2.2 Secondary objective

To evaluate the safety and tolerability of macitentan in patients with symptomatic PAH.

2.3 Exploratory objectives

To investigate the effect of macitentan on disease-related circulating biomarkers in patients with symptomatic PAH.

To explore a potential association between change in right ventricular properties and clinical outcome in patients with symptomatic PAH.

To investigate the effect of macitentan on ventriculo-arterial coupling in patients with symptomatic PAH.

To evaluate the effect of macitentan on LV properties in patients with symptomatic PAH.

2.4 Sub-studies rationale and objectives

2.4.1 Metabolism sub-study (in selected US sites only)

2.4.1.1 Rationale

In PAH, right ventricle hypertrophy causes a greater oxygen requirement. This induces an adaptation of the metabolic pathways by a shift from fatty acid to glucose consumption [Archer 2013]. Glucose consumption can be assessed by Positron Emission Tomography (PET) [Bokhari 2011].

2.4.1.2 Objectives

To assess the effect of macitentan on cardiac and arterial metabolism in patients with symptomatic PAH by PET-MR imaging.

2.4.2 Biopsy sub-study

2.4.2.1 Rationale for taking biopsies

Right ventricular remodeling is associated with tissue changes such as fibrosis, capillary rarefaction and with changes at the cellular and sub-cellular level, for example changes in cardiomyocyte size and mitochondrial morphology. In addition, there are expression changes in the messenger RNA (mRNA) encoding receptor and enzyme proteins and expression changes in functionally important proteins.

Biopsies may bring complementary information that could not be obtained by other means. There are inherent risks to biopsies of the endomyocardium of the interventricular septum, such as perforation of the septum. Risks are further mitigated here by involving only sites with solid experience in this sub-study. Therefore, the risks are deemed acceptable.

2.4.2.2 Rationale for mRNA transcript analysis

The functioning of cells is governed by proteins such as enzymes, receptors or hormones. mRNA transcript analysis allows the identification of proteins synthetized in cells.

In this study, mRNA transcript analysis is performed both in endomyocardial cells and in peripheral blood mononuclear cells (PBMC) in order to compare proteins and expressed mRNA in PBMC with those expressed in the endomyocardial cells and to test the hypothesis that the expression pattern of the peripheral circulating PBMC may reflect changes observed in the endomyocardium and thus serve as a surrogate for the heart tissue sample in the assessment of targets influenced by macitentan treatment.

2.4.2.3 Objectives

To assess the histological and biochemical effects of macitentan on the endomyocardium of the interventricular septum in patients with symptomatic PAH.

To assess the biochemical effects of macitentan on PBMC in patients with symptomatic PAH.

2.4.3 Echo sub-study

2.4.3.1 Rationale

Three-dimensional (3D), 2-dimensional (2D), M-mode and Doppler echocardiography allow to assess the geometry and function of the right and left ventricles, thereby offering the potential to further extend the knowledge of the effects of macitentan on the heart in PAH.

2.4.3.2 Objective

To assess the effect of macitentan on right and left ventricular function by echocardiography in patients with symptomatic PAH.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, single-arm, open-label, Phase 4 study to evaluate the effects of macitentan on right ventricular remodeling in PAH assessed by cardiac magnetic resonance imaging.

One hundred patients will be enrolled in approximately 50 sites in approximately 12 countries in Asia, Australia, Europe, and North America. Enrollment will be competitive across participating sites.

The study consists of the following time points and periods:

Screening commences from signature of the Informed Consent Form (ICF) and ends with study treatment initiation (up to 28 days after informed consent signature).

Baseline: baseline values are those from the inclusion RHC and those collected during screening or at Treatment Initiation Visit (Day 1) before initiation of study treatment.

Treatment Period starts with the 1st dose of study drug (Day 1 of study) and ends with EOT on the day of the last dose of study drug which is at premature discontinuation of study drug or Week 52 ± 7 days. For patients prematurely discontinuing study drug, an EOT visit must be organized as soon as possible and no later than 7 days after the decision to end study treatment.

The Safety follow-up period starts immediately after the last dose of study drug and ends 30 to 37 days after EOT, with End of Study (EOS) Visit. For patients who withdraw their consent, the investigator will seek agreement to conduct the safety follow-up.

EOS for a patient is the end of safety follow-up, or date of death, or date of consent withdrawal, or date of last contact for patients lost to follow-up.

Sub-studies

As part of this protocol, three sub-studies will be conducted in selected centers. In these centers, all patients eligible for the main study will be offered to participate in the sub-study(ies).

1. Metabolism sub-study (selected US sites only).

2. Biopsy sub-study.

3. Echo sub-study.

Study Duration

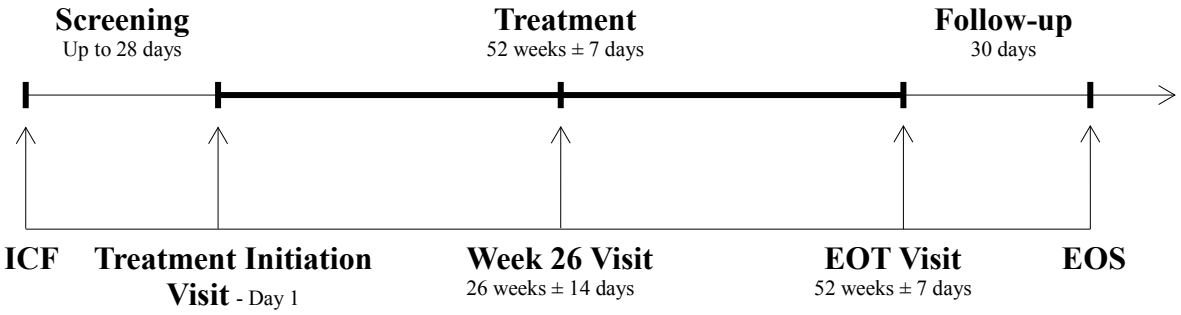
For an individual patient, treatment duration will be up to 371 days. Patient participation in the study will be approximately 14 months. Once the study treatment is finished, patients will receive local standard medical care.

The overall study ends with the last patient's last visit.

An interim analysis will be conducted when 42 patients have available assessment data for both primary endpoints. If the interim analysis concludes that the study is positive on both primary endpoints, enrollment may stop. Otherwise, the study will continue until 100 patients are enrolled. The decision to stop or continue the study will be taken jointly by the Steering Committee and the sponsor, considering statistical analysis results as well as clinical expertise.

The overall study design is depicted in Figure 1.

Figure 1 Study design



ICF, informed consent form (signature); EOT, end of treatment; EOS, end of study.

3.2 Study design rationale

Cardiac MRI allows the assessment of right ventricular geometry and function, with a low between-study [Grothues 2003, Bradlow 2010] and between-observer [Bradlow 2010] variability. It is, therefore, the method of choice for assessing right ventricular remodeling.

Non-controlled, open-label trials are classically used in imaging studies that assess cardiac changes in PAH [Wilkins 2005, Van Wolferen 2006, Hinderliter 1997, Roeleveld 2004, Blalock 2010, Peacock 2014].

Open-label trials have a potential for bias. Bias in the assessment of the primary endpoint is reduced by the use of objective measurements.

Objectivity of cardiac MRI images assessment is ensured by central assessment of images by assessors who are blinded to the patient and time point of the cardiac MRI, i.e., before or during treatment. Since PAH is a progressive disease, a reverse remodeling is not expected to be observed unless it is induced by a treatment. Therefore, patients may be used as their own control, i.e., a patient's post-baseline values may be compared to the corresponding baseline values.

To ensure that the effects observed on the right ventricle are due to the newly introduced treatment, eligibility criteria are designed to select for:

- Treatment-naïve patients, who may initiate macitentan alone or combined with a PDE-5 inhibitor;
- And patients on a stable dose of PDE-5 inhibitors, who will initiate macitentan only.

The primary endpoint is defined at 26 weeks because it is deemed late enough to observe a relevant change and early enough to have a relatively low proportion of patients

dropping out for the primary endpoint, either by discontinuing study treatment or by initiating additional PAH therapy.

The endpoints defined at 52 weeks aim to determine whether the treatment effect at 26 weeks is maintained at 52 weeks.

3.3 Site personnel and their roles

- The site physician will conduct physical examinations.
- The site physician or nurse will administer the 6-minute walk test (6MWT).
- Study-mandated RHCs will be performed by an experienced cardiologist or surgeon designated by the site.
- Cardiac MRI will be performed by an experienced imaging specialist designated by the site.

In the corresponding sub-studies:

- PET-MR scan will be done by an experienced imaging specialist designated by the site.
- The biopsy will be done by the person conducting the RHC.
- Echo will be done by a specialist designated by the site.

3.4 Study committees

3.4.1 Steering Committee

A Steering Committee is involved in the design of the study, will provide guidance on study conduct and interpretation of results, and will support study publications. The committee is governed by a steering committee charter.

3.4.2 Central imaging

Central imaging committees composed of trained imaging specialists have been appointed by Actelion to assess the following variables according to a dedicated charter:

- Cardiac MRI results: (analyzed by the Image Analysis Center [IAC]).
- Pressure-volume relationships (analyzed by the IAC).
- Variables that are specific to the metabolism sub-study.
- Echo results.

3.4.3 Independent Liver Safety Data Review Board

An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) provides ongoing assessment and advice regarding serious hepatic adverse events of special interest (HAESI) that require further evaluation during the study (as per ILSDRB charter).

4 PATIENT POPULATION

4.1 Patient population description

Adult and elderly patients will be enrolled with idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, PAH associated with connective tissue disease or PAH associated with congenital heart diseases under certain conditions [see Section 4.3].

It is planned to enroll 100 patients. In case of insufficient recruitment, additional sites may be invited to participate in the study.

4.2 Rationale for the selection of the study population

Patients included must have WHO group I PAH, in accordance with the approved indication for macitentan. The PAH etiologies selected have very similar characteristics, although patients with PAH associated with connective tissue disease suffer from diverse comorbidities and their prognosis is worse [Benza 2010, Fisher 2006]. In systemic sclerosis, right ventricular function is more depressed [Hassoun 2009, Tedford 2013, Fisher 2006] with a lower contractility [Overbeek 2008]. The prevalence of pericardial effusion is also higher [Fisher 2006]. Despite the specificities of PAH associated with connective tissue disease, recent data using cardiac MRI have shown a significant treatment effect of combination therapy in a sub-population of patients with PAH associated with connective tissue disease without significant restrictive or obstructive lung disease [Hassoun 2015].

Furthermore, previous PAH treatments are limited to PDE-5 inhibitors only, in order to capture the full effect of the newly added treatment. The absence of clinically relevant interaction between macitentan and the PDE-5 inhibitor sildenafil and its metabolite (N-desmethyl-sildenafil) has been shown [Macitentan IB].

The study population is, therefore, expected to be relatively homogeneous and suitable to achieve the study objectives.

4.3 Inclusion criteria

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

1. Signed informed consent prior to any study-mandated procedure.
2. Symptomatic PAH.
3. WHO FC I to III.
4. PAH etiology belonging to one of the following groups according to Nice classification:
    1.1 Idiopathic PAH
    1.2 Heritable PAH

1.3 Drug- and toxin-induced PAH
1.4.1 PAH associated with connective tissue disease
1.4.4 PAH associated with congenital heart diseases: **only simple** (atrial septal defect, ventricular septal defect, patent ductus arteriosus) **congenital systemic to pulmonary shunts at least 2 year post surgical repair.**

5. Hemodynamic diagnosis of PAH confirmed by RHC performed between Day −28 and Day 1 (inclusion RHC; RHC data obtained at study site within this time frame, prior to obtaining signed informed consent, are acceptable) showing:
   - mPAP ≥ 25 mmHg *and*
     - Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 12 mmHg and PVR ≥ 4WU (320 dyn.sec.cm^{-5}) *or*
     - 12 mmHg ≤ PCWP or LVEDP ≤ 15 mmHg and PVR ≥6 WU (480 dyn.sec.cm^{-5}).
6. 6MWD ≥ 150 m during screening.
7. For patients treated with oral loop diuretics, treatment dose must have been stable at least 1 month prior to the inclusion RHC.
8. For patients treated with PDE-5 inhibitors, treatment dose must have been stable at least 3 months prior to the inclusion RHC (initiation of PDE-5 inhibitors during screening is allowed after all screening assessments have been performed).
9. For patients treated with beta blockers, treatment dose must have been stable at least 1 month prior to the inclusion RHC.
10. Men or women ≥ 18 and < 75 years. For patients aged ≥ 65 and < 75 years, an eligibility form [Appendix 7] will be submitted to a Steering Committee member who will reserve the right to exclude the patient.
11. Women of childbearing potential [see Section 4.5.1] must:
    a. Have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day 1, *and*
    b. Agree to use reliable methods of contraception [see Section 4.5] from screening up to 30 days after study treatment discontinuation, *and*
    c. Agree to perform monthly pregnancy tests up to 30 days after study treatment discontinuation.

4.4 Exclusion criteria

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

1. Body weight < 40 kg.
2. Body mass index (BMI) > 35kg/m^2. For patients with 30kg/m^2 < BMI < 35kg/m^2, an eligibility form will be submitted to a Steering Committee member who will reserve the right to exclude the patient [Appendix 7].

3. Pregnancy, breastfeeding, or intention to become pregnant during the study.
4. Recently started (< 8 weeks prior to informed consent signature) or planned cardio-pulmonary rehabilitation program.
5. Known concomitant life-threatening disease with a life expectancy < 12 months.
6. Any condition likely to affect protocol or treatment compliance.
7. Hospitalization for PAH (except for diagnosis of PAH) within 3 months prior to informed consent signature.
8. Left atrial volume indexed for body surface area (BSA) ≥ 43mL/m^2 by echocardiography or cardiac MRI.
9. Moderate to severe left-heart valvular disease.
10. History of pulmonary embolism or deep vein thrombosis.
11. 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 (eligible only if no or mild interstitial lung disease on computed tomography).
    - FVC < 60% of predicted.
    - Forced expiratory volume in one second (FEV_1) < 60% of predicted.
12. Moderate to severe restrictive lung disease (i.e., total lung capacity < 60% of predicted value) at any time prior to enrollment.
13. Historical evidence of significant coronary artery disease established by:
    - History of myocardial infarction *or*
    - More than 50% stenosis in a coronary artery (by percutaneous coronary intervention or angiography) *or*
    - Elevation of the ST segment on electrocardiogram *or*
    - History of coronary artery bypass grafting *or*
    - Stable angina.
14. Known uncontrolled diabetes mellitus (in the opinion of the investigator).
15. Severe renal insufficiency (calculated creatinine clearance < 30 mL/min).
16. Cancer.
17. Systolic blood pressure < 90 mmHg.
18. Severe hepatic impairment (with or without cirrhosis) according to National Cancer Institute organ dysfunction working group criteria, defined as total bilirubin > 3 × ULN accompanied by an AST elevation > ULN at screening
19. Hemoglobin < 100 g/L.
20. Serum AST and/or ALT > 3 × ULN.
21. Need for dialysis.
22. Responders to acute vasoreactivity test based on medical history.
23. Prior use of ERAs, stimulators of soluble guanylate cyclase or prostacyclin or prostacyclin analogs.

24. Treatment with strong inducers of cytochrome P450 isozyme 3A4 (CYP3A4) within 4 weeks prior to study treatment initiation (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort).
25. Treatment with strong inhibitors of CYP3A4 within 4 weeks prior to study treatment initiation (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir).
26. Treatment with another investigational drug (planned, or taken within the 3 months prior to study treatment initiation).
27. Hypersensitivity to any ERA or any excipients of the formulation of macitentan (lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, polyvinyl alcohol, polysorbate, titanium dioxide, talc, xanthan gum, and lecithin soya).
28. Claustrophobia.
29. MRI-incompatible permanent cardiac pacemaker, automatic internal cardioverter.
30. Metallic implant (e.g., defibrillator, neurostimulator, hearing aid, permanent use of infusion device).
31. Atrial fibrillation, multiple premature ventricular or atrial contractions, or any other condition that would interfere with proper cardiac gating during MRI.
32. **For patients enrolling in the metabolism sub-study only:** glucose intolerance.
33. **For patients enrolling in the biopsy sub-study only:** PAH etiology belonging to Nice classification 1.4.4: PAH associated with congenital heart diseases or 1.4.1: PAH associated with connective tissue disease.

4.5 Reliable contraception for women of childbearing potential

4.5.1 Definition of woman of childbearing potential

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

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

4.5.2 Europe and Asia

The 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 (IUD), *or*
2. True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the patient, *or*

3. Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to screening), *or*
4. Sterilization of the male partner, with documented post-vasectomy confirmation of the absence of sperm in the ejaculate.

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

4.5.3 North America and Australia

The 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 Patient population in sub-studies

4.6.1 Metabolism sub-study

Between 10 and 30 patients enrolled in the main study will also be enrolled in the metabolism sub-study. For this sub-study, patients with glucose intolerance are excluded because the tracer used for PET-MR imaging is a glucose analog, contra-indicated in these patients.

4.6.2 Biopsy sub-study

Between 10 and 20 patients enrolled in the main study will also be enrolled in the biopsy sub-study. For this sub-study, patients with PAH etiology belonging to Nice classification 1.4.4 (PAH associated with congenital heart diseases) or 1.4.1 (PAH associated with connective tissue disease) are excluded because their endomyocardium presents differences from the endomyocardium in the other etiologies enrolled in the study.

4.6.3 Echo sub-study

Between 40 and 50 patients enrolled in the main study will also be enrolled in the Echo sub-study.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment: description and rationale

The study treatment is macitentan 10 mg, for once daily oral administration.

The dose and regimen are in accordance with product labeling. The efficacy and safety of macitentan 10 mg in patients with PAH were demonstrated in the AC-055-302 / SERAPHIN study [Pulido 2013]. The risk of a morbidity/mortality event was reduced by 45% with macitentan 10 mg compared to placebo ($p < 0.0001$), and the treatment was well tolerated. Further details can be found in Section 1.2.2.4 and in the IB [Macitentan IB].

5.1.2 Study treatment administration

One tablet of macitentan 10 mg must be taken once daily orally, preferably at the same time of the day. Macitentan can be taken with or without food.

Up- or down-titration does not apply. If a dose is missed, the patient must take it as soon as possible that day and take the next dose at the next scheduled time. The patient should not take two doses at the same time if a dose has been missed.

Study assessments will be performed at trough [see Section 7].

5.1.3 Treatment assignment

All patients will receive open-label macitentan 10 mg once daily.

5.1.4 Patient identification

When screening a patient, the investigator/delegate contacts the Interactive Response Technology (IRT) system which assigns a **patient number** to the patient. The patient number consists of 4 digits identifying the site and 3 digits identifying the patient, e.g., 1234567.

After having confirmed a patient's eligibility, and prior to study treatment initiation, the investigator/delegate contacts the IRT system which assigns a treatment kit number to the patient.

5.1.5 Blinding

Not applicable.

5.1.6 Study treatment supply

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

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

5.1.6.1 Study treatment packaging and labeling

5.1.6.1.1 Study treatment packaging

Study treatment is provided as tablets and supplied in childproof bottles containing 36 tablets each (1 month supply). At Treatment Initiation Visit and Week 26 visit, six bottles will be provided to the patients.

5.1.6.1.2 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.

Each medication bottle will have a label with a tear-off part specifying study protocol number, batch number, and bottle number. When study medication is issued to the patient, the investigator, pharmacist (if applicable), or designee must remove the tear-off part and attach it to the Investigational Medicinal Product Label Dispensing Log.

5.1.6.2 Study treatment storage and distribution

Treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the medication labels. Detailed instructions regarding the handling and storage of study treatment are provided in Appendix 5.

5.1.6.3 Study treatment dispensing

Patients will receive sufficient study treatment to cover the period up to the next scheduled visit. Patients are asked to return all used, partially used and unused study bottles at each visit. The protocol-mandated study drug 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 patient must be available for inspection at any time.

5.1.6.4 Study treatment return and destruction

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

5.1.7 Compliance with study treatment

Study treatment accountability must be performed by the study staff on the day of the visit and before providing further study treatment, in order to ensure that the patient is compliant with study requirements. Study treatment accountability is recorded in the Case Report Form (CRF) and checked by the monitor during site visits and at the end of the study.

Compliance is based on study treatment accountability.

$$\text{Compliance} = \frac{(\text{number of tablets provided to patient} - \text{number of tablets returned})}{\text{Total number of Tablets that should have been taken during the period)}} \times 100$$

Compliance with study treatment intake < 80% or > 120% will be considered a deviation from the protocol.

5.1.8 Study treatment interruptions

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.10.

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

Interruptions of study treatment must be kept as short as possible, and must be recorded in the CRF. An interruption for more than 4 consecutive weeks will lead to permanent treatment discontinuation.

5.1.9 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the patient, the investigator, or Actelion.

A patient has the right to prematurely discontinue study treatment at any time by withdrawal from treatment only or by withdrawal from treatment and any further participation in the study.

A patient enrolled in a sub-study may discontinue either the sub-study only, or both the study and the sub-study.

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

Premature discontinuation of study treatment may also result from a decision by Actelion, e.g., in case of premature termination or suspension of the study [see Section 9.3].

Study treatment may be discontinued in response to an AE, lack of efficacy (including disease progression, treatment failure, worsening of patient condition), a protocol deviation (e.g., non-compliance with study requirements, such as non-compliance with study treatment intake or visit attendance), or if the patient is lost to follow-up. study-specific criteria for discontinuation of study treatment are described in Section 5.1.10.

The main reason and whether discontinuation of study treatment is the decision of the patient, the investigator, or Actelion must be documented in the CRF.

A patient who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until 30 to 37 days after EOT, provided that the patient's consent for this limited participation in the study has not been withdrawn. Patients prematurely discontinuing study treatment will be asked to return for a Premature EOT Visit within 7 days of decision to end study treatment. The EOS visit will take place 30 to 37 days after EOT.

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

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

5.1.10.1 Pregnancy

If a female patient becomes pregnant while on study drug, study drug must be discontinued immediately, and a Pregnancy Form must be completed [see Section 10.3].

5.1.10.2 Liver aminotransferases abnormalities

Interruption of study drug

Study drug must be interrupted in the following cases:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and ≤ 8 × ULN without associated clinical symptoms of liver injury and without associated increase in total bilirubin ≥ 2 ×ULN.

In such a case, a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase must be performed within one week. If AST and/or ALT elevation is confirmed, monitoring of aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be continued 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 study treatment can be considered.

Interruptions must be for less than 4 consecutive weeks; longer interruptions must lead to permanent discontinuation of study drug.

Reintroduction of study treatment after treatment interruption should only be considered if the potential benefits of treatment with macitentan 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 then be checked within 3 days after reintroduction, then again after a further 2 weeks and thereafter according to the protocol [Section 7.3.5.2].

Permanent discontinuation of study drug

Study drug must be stopped and its reintroduction is not to be considered in the following cases:

- Aminotransferases > 8 × ULN.
- Aminotransferases ≥ 3 × ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, anorexia, dark urine, itching, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever).
- Aminotransferases ≥ 3 × ULN and associated increase in total bilirubin ≥ 2 ×ULN.

In such cases, aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study drug 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) must be considered and ruled out by performing the appropriate tests.

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

An ILSDRB (an external expert committee of hepatologists) provides ongoing assessment and advice regarding serious HAESI that require further evaluation during the study (as per ILSDRB charter).

5.1.10.3 Hemoglobin abnormalities

In case of hemoglobin decrease from baseline[1] of > 20 g/L, a retest must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

- Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration).
- Peripheral blood smear.
- Reticulocyte count.
- Iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation).
- Lactate dehydrogenase.
- Indirect bilirubin.

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

- A decrease in hemoglobin to < 80 g/L (< 4.9 mmol/L).
- A decrease in hemoglobin from baseline[1] of > 50 g/L.
- The need for transfusion.

Reintroduction of study medication may be considered if hemoglobin recovery, defined as a return of hemoglobin above the lower limit of the normal range (LLN) or if it returns to a value close to that at baseline.

Interruption of study medication must not last longer than 4 consecutive weeks; longer interruptions must lead to permanent discontinuation of study drug.

[1] Baseline hemoglobin: last value obtained prior to first intake of study treatment.

5.1.10.4 Start of an ERA / strong CYP3A4 inducer or inhibitor / investigational drug

Study drug must be permanently discontinued if another ERA and/or a strong CYP3A4 inducer and/or a strong CYP3A4 inhibitor and/or another investigational drug is started during treatment period.

5.2 Previous and concomitant therapy

5.2.1 Definitions

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

A therapy that is study-concomitant is any treatment that is either ongoing at informed consent signature or initiated thereafter, up to 30 days after the end of study treatment.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the initiation of study treatment or is initiated thereafter, up to 30 days after the end of study treatment.

Concomitant treatments of special interest are those susceptible to influence PAH disease, namely PAH-specific therapies and loop diuretics. These therapies are allowed at baseline under certain conditions [see Section 4.3]. Initiation of these therapies or up-titration of PDE-5 inhibitors before Week 26 is allowed only in case of disease progression [see Section 5.2.5], except for patients naïve to PAH treatment who are allowed to initiate and titrate a PDE-5 inhibitor within 2 weeks of study drug initiation [see Section 5.2.3.1].

5.2.2 Reporting of previous/concomitant therapy in the CRF

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

Previous therapy must be recorded in the CRF if discontinued less than 3 months prior to study treatment initiation.

For all therapy, the generic name, start/end dates of administration (as well as whether it was ongoing at study treatment initiation and/or EOS), route, dose, and indication will be recorded in the CRF.

For the following therapies, treatment dose and every dose change must be recorded in the CRF:

- Loop diuretics.
- PDE-5 inhibitors.

- Prostanoid analogs by any route of administration.
- Stimulators of soluble guanylate cyclase.
- Beta-blockers.
- Any other PAH-specific therapy that may obtain marketing authorization during study conduct.

5.2.3 Allowed concomitant therapy

5.2.3.1 Until Week 26 RHC

The following therapies are allowed until Week 26 RHC:

- Therapies allowed at baseline based on eligibility criteria [see Sections 4.3 and 4.4].
- Oral loop diuretics if used at a stable dose for 1 week prior to Week 26 RHC.
- Use of rescue therapy [see Section 5.2.5] only in case of disease progression.
- A PDE-5 inhibitor may be initiated from the time when all screening assessments have been performed until Day 14, provided that dose optimization is complete at the latest 14 days after study treatment initiation.

5.2.3.2 After Week 26 RHC

After Week 26 RHC, treatment initiation and dose changes are allowed for:

- Loop diuretics.
- PDE-5 inhibitors.
- Prostanoid analogs by any route of administration.
- Stimulators of soluble guanylate cyclase.
- Any other PAH-specific therapy that may obtain marketing authorization during study conduct.

5.2.4 Forbidden concomitant therapy

Therapies acting though the same therapeutic pathway as study drug are forbidden:

- ERAs other than study drug.

Therapies that are not well characterized are forbidden:

- Investigational drug other than study drug.

Therapies altering the exposure to study drug are forbidden to avoid under- and over-dose [Macitentan IB, section 1.7.2]:

- Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir).
- Strong inducers of CYP3A4 (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort).

Initiation of one of these prohibited medications will lead to premature discontinuation of study treatment.

Disease-specific treatments are forbidden, except in specific situations, since they would interfere with efficacy evaluation [Section 5.2.5].

5.2.5 Rescue therapy before Week 26 RHC

The following treatment changes are allowed before Week 26 RHC only in case of disease progression:

- Initiation of:
  - i.v. loop diuretics.
  - PDE-5 inhibitors.
  - Prostanoid analogs by any route of administration.
  - Stimulators of soluble guanylate cyclase.
  - Any other PAH-specific therapy that may obtain marketing authorization during study conduct.
- Up-titration of PDE-5 inhibitors.

Use of these treatments does not require study treatment discontinuation.

Disease progression is defined as:

- Decrease in 6MWD by more than 15% associated with worsening in WHO FC, *or*
- Need for s.c. or i.v. prostanoid therapy, *or*
- Hospitalization for PAH (investigator's assessment).

Disease progression must be recorded as an AE in the CRF. Decreases in 6MWD > 15% from baseline in conjunction with worsening WHO FC that occur between scheduled visits and do not result in a rescue therapy initiation (RTI) visit must be recorded in the electronic CRF (eCRF) using an unscheduled visit form.

After Week 26 RHC, treatment changes are allowed.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoints

The study has two primary efficacy endpoints:

- Change from baseline to Week 26 in Right Ventricular (RV) Stroke Volume (RVSV) assessed by cardiac MRI from pulmonary artery flow.
- Ratio of Week 26 to baseline PVR assessed by RHC.

RVSV is determined by the IAC. Assessors are blinded to the patient identity and to the date of image acquisition.

RVSV indexed for BSA was shown to predict outcome [Van Wolferen 2007]. RVSV quantifies blood flow independently of heart rate (HR). An increase in RVSV would reflect a favorable, reverse remodeling of the right ventricle and is expected to reduce PAH symptoms through a better oxygenation.

A decrease in PVR appears as the primary direct effect expected from a PAH therapy. Furthermore it is an objective measurement of disease progression.

The primary endpoint is defined at 26 weeks because it is deemed late enough to observe a relevant change and early enough to have a relatively low proportion of patients dropping out for the primary endpoint, either by discontinuing study treatment or by initiating additional PAH therapy.

6.1.2 Secondary efficacy endpoints

In the same way as the primary endpoints, secondary endpoints are assessed at 26 weeks. They consist of characteristics of the right ventricle, and of widely accepted tools to assess PAH progression:

Change from baseline to Week 26 in:

- RV End Diastolic Volume (RVEDV)
- RV End Systolic Volume (RVESV)
- RV Ejection Fraction (RVEF)
- RV mass
- 6MWD
- WHO FC

MRI variables will be assessed by the IAC.

6.1.3 Exploratory efficacy endpoints

The following endpoints are usual tools to monitor disease progression or treatment response and will be assessed:

Change from baseline to Week 26 in:

- mPAP
- Mean right atrial pressure (mRAP)
- Cardiac index
- Arterial elastance
- RV end-systolic elastance
- RV maximum isovolumic pressure

The following exploratory endpoints aim to determine whether the treatment effect at 26 weeks is maintained at 52 weeks. Primary and secondary endpoints are repeated at 52 weeks except for variables assessed by RHC since this procedure is not performed at 52 weeks.

Change from baseline to Week 52 in:

- RVSV determined by cardiac MRI from pulmonary artery flow
- RVEDV
- RVESV
- RVEF
- RV mass
- 6MWD
- WHO FC

Variables pertaining to the left ventricle will also be assessed, at 26 weeks and 52 weeks.

Change from baseline to Week 26 and Week 52 in:

- Stroke Volume determined by cardiac MRI from the aortic flow
- LV End Diastolic Volume (LVEDV)
- LV End Systolic Volume (LVESV)
- LV Ejection Fraction (LVEF)
- LV mass
- RVEDV/LVEDV
- RVESV/LVESV

MRI variables and variables determined from pressure-volume relationship will be assessed by the IAC.

The following exploratory endpoints aim to investigate potential simple methods for disease monitoring, as opposed to RHC, MRI or echocardiography:

Change from baseline to Week 26 and Week 52 in:

- N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Uric acid
- Red cell distribution width
- Activin A
- Cystatin C
- Follistatin
- Galectin-3
- Growth Differentiation Factor (GDF)-15
- Cardiac troponin T

- Lactate dehydrogenase (LDH)
- Osteoprotegerin
- Tumor Necrosis Factor (TNF) alpha

These variables will be assessed by the central laboratory.

The following endpoint is designed to investigate patient outcome.

- Time to first clinical worsening event defined as:
  - Decrease in 6MWD by > 15% from baseline associated with worsening in WHO FC, *or*
  - Initiation of s.c. or i.v. prostanoid therapy, *or*
  - Hospitalization for PAH (investigator's assessment), *or*
  - Death.

6.2 Safety endpoints

- Treatment-emergent AEs up to 30 days after EOT.
- Treatment-emergent SAEs up to 30 days after EOT.
- AEs leading to premature discontinuation of study drug.
- Treatment-emergent marked laboratory abnormalities up to 30 days after EOT.
- Occurrence of liver function test ([LFT] ALT and/or AST) abnormality (≥ 3; ≥ 3 and < 5 × ULN; ≥ 5 and < 8 × ULN; ≥ 8 × ULN) up to EOT.
- Occurrence of hemoglobin abnormality (≤ 80 g/L; > 80 and ≤ 100 g/L) up to EOT.
- Occurrence of ALT and/or AST abnormality ≥ 3 × ULN associated with bilirubin ≥ 2 × ULN.

6.3 Exploratory endpoints in sub-studies

6.3.1 Metabolism sub-study

Exploratory endpoints:

- Change from baseline to Week 26 and to Week 52 in:
  - RV ^{18}F-fluorodeoxyglucose (FDG) uptake
  - Aortic ^{18}F-FDG uptake
  - Right common carotid ^{18}F-FDG uptake
  - Left common carotid ^{18}F-FDG uptake

All variables that are specific to the metabolism sub-study will be centrally assessed according to a charter.

6.3.2 Biopsy sub-study

Exploratory endpoints:

- Change from baseline to Week 26 in:
  - Qualitative assessment of endomyocardium function markers in biopsies
  - Relative quantitative assessment of endomyocardium function markers in biopsies
  - Number of capillaries per cardiomyocyte
  - Mean cardiomyocyte volume
  - Qualitative assessment of cardiomyocytes
  - Endomyocardium cells mRNA transcript analysis
  - PBMC mRNA transcript analysis

Biopsy and blood samples will be analyzed by the central laboratory.

6.3.3 Echo sub-study

Exploratory endpoints:

- Change from baseline to Week 26 and Week 52 in:
  - LV eccentricity index at end-diastole
  - LV eccentricity index at end-systole
  - Minimum diameter of the inferior vena cava (at inspiration)
  - Maximum diameter of the inferior vena cava (at end-expiration)
  - Tricuspid annular plane systolic excursion (TAPSE)
  - Pericardial effusion size scored from 0 to 4
  - RV acceleration time, by tissue Doppler and pulsed wave Doppler
  - RV ejection time, by tissue Doppler and pulsed wave Doppler
  - Total RV Systolic Time (duration of tricuspid insufficiency jet)
  - Doppler RV index (RV myocardial performance index), by tissue Doppler and pulsed wave Doppler
  - Tricuspid peak jet velocity
  - RV systolic pressure (estimated by tricuspid valve Doppler)
  - Early diastolic velocity of the jet of pulmonary valve regurgitation
  - End-diastolic velocity of the jet of pulmonary valve regurgitation
  - Cardiac output determined from LV outflow tract
  - Mitral E-wave velocity
  - Mitral A-wave velocity
  - Mitral annulus peak early diastolic velocity E’
  - E/A ratio
  - E/E’ ratio
  - 2D RV dimension end-diastole
  - Tricuspid peak annular velocity s’
  - RV end diastolic area

- RV end systolic area
- RV fractional area change
- RVSV determined from pulmonary valve Doppler and pulmonary annulus dimension
- Tricuspid peak E, peak A, deceleration time
- Tricuspid peak diastolic annular velocities e', a'
- LVEDV determined from 2D measurements
- LVESV determined from 2D measurements
- Mitral deceleration time
- Mitral annular plane tissue Doppler velocity a'
- 2D Global Longitudinal RV strain
- 2D circumferential RV strain
- Time to peak RV strain
- RVSV
- RVEDV
- RVESV
- RVEF
- RV mass
- Left Ventricular Stroke Volume (LVSV)
- LVEDV
- LVESV
- LVEF
- LV mass
- RVEDV/LVEDV
- RVESV/LVESV

In this study protocol, Echo refers to 3D, 2D, M-mode and Doppler echocardiography. All Echo results will be centrally assessed according to a charter.

7 STUDY ASSESSMENTS

All study assessments will be performed at trough. During site visits, patients will be instructed to take their daily study medication after all study assessments have been made.

All study assessments are performed by a qualified study staff member: medical, nursing, or specialist technical staff, and are recorded in the CRF, unless otherwise specified. Study assessments performed during unscheduled visits (RTI, premature EOT, other unscheduled visit) will also be recorded in the CRF.

If the principal investigator delegates any study procedure/assessment for a patient, e.g., RHC, MRI, blood sampling, etc., to an external facility, he/she must 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 under the responsibility of the principal investigator.

Calibration certificates for the following devices used to perform study assessments must be available prior to the enrollment of the first patient:

- Temperature measurement devices for study medication storage area and freezer.

7.1 Screening/baseline assessments

7.1.1 Eligibility criteria

Eligibility criteria will be collected in the CRF.

7.1.2 Demographic and baseline characteristics

The following baseline variables will be collected in the CRF during the screening period for all screened patients:

- Age, gender, height, weight.
- Race if allowed by local regulations.
- PAH etiology, age at PAH diagnosis.

7.1.3 Medical history

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

- Complications or symptoms associated with PAH (e.g., peripheral edema or right heart failure)
- Any chronic conditions (e.g., diabetes, hypertension, angina pectoris)
- Acute conditions present at screening or which occurred in the past with sequelae
- Any serious condition in the past resolved without sequelae (e.g., acute peritonitis)

7.1.4 Medications

Previous [see Section 5.2.2] and concomitant medications must be recorded in the CRF. Each treatment taken by the patient must be matched by a corresponding symptom or condition in medical history (except prophylactic treatments).

7.1.5 Birth control methods

For women of childbearing potential [see Section 4.3], birth control methods must be recorded in the CRF.

7.1.6 6-minute walk test

The 6MWT is a non-encouraged test which measures the distance covered over a 6-minute walk [ATS Statement 2002]. The Borg dyspnea index is evaluated after each 6MWT. It rates dyspnea on a scale from '0' to '10' [Appendix 3].

Detailed guidelines on correct execution of these tests 'Actelion guidelines for 6MWT' [Appendix 2] must be followed. For patients who have never performed a 6MWT previously, a training test will be requested before the qualifying test for inclusion.

7.1.7 WHO Functional Class

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

7.1.8 Cardiac MRI

Images will be taken in accordance with the **Cardiac MRI image acquisition protocol** and uploaded to the Central Image Repository (CIR) through a dedicated web application or sent to the CIR by courier (on a CD). A quality check will be performed as soon as the data sets are received.

The actual assessments will be done on data sets blinded to the patient identity and to the date of image acquisition, and only after a patient's study completion or withdrawal. An exception to this rule will be made for patients analyzed for the interim analysis and who have not yet completed the study or withdrawn. For these patients, available images will be analyzed at the time of interim analysis.

All sets of images for each patient will be assessed at the same time by the same assessor, in order to ensure rigorously consistent assessment. Thus, patients analyzed for the interim analysis and who have not yet completed the study or withdrawn will be analyzed twice if new images become available:

- Available images will be analyzed at interim analysis, and the results used for the interim analysis.
- All images will be analyzed at final analysis, and the results used for the final analysis.

The IAC will assess the following variables according to a dedicated charter and the results will be sent to Actelion:

- RVSV determined from pulmonary artery flow
- RVEDV
- RVESV
- RVEF
- RV mass
- LVSV determined from aortic flow
- LVEDV
- LVESV

- LVEF
- LV mass
- RVEDV/LVEDV
- RVESV/LVESV

7.1.9 Right heart catheterization

The Actelion guidelines for RHC [Appendix 1], including formulas, will be followed. Digitally sampled right ventricle pressure curve and pulmonary artery pressure curve, simultaneous with ECG sampling, must be recorded. The record must cover at least 10 cardiac cycles. Sample frequency must be at least 200Hz. Calibration must be provided. The curves will be uploaded to the CIR through a dedicated web application, and blinded to the patient identity as well as to the date of acquisition.

Where electronic recording of pressure curves is not possible at a site, alternative solutions will be determined on a case by case basis before any patient can be enrolled.

The following variables will be determined locally and entered in the CRF:

- PVR
- mPAP
- Systolic pulmonary artery pressure (sPAP)
- Diastolic pulmonary artery pressure (dPAP)
- PCWP or LVEDP
- mRAP
- Cardiac output (CO)
- HR during RHC
- Systolic systemic artery pressure (sSAP)
- Diastolic systemic artery pressure (dSAP)
- The date of RHC will be entered in the CRF

7.1.10 Pressure-volume relationship

The IAC will assess pressure-volume relationship based on cardiac MRI results and RHC pressure curves.

The IAC will assess the following variables according to a dedicated charter and the results will be sent to Actelion:

- Arterial elastance
- RV end-systolic elastance
- RV maximum isovolumic pressure

The methods used to determine these variables will be described in a charter.

7.1.11 Blood tests

Blood samples will be taken and analyzed by a central lab. These analyses are listed in Section 7.3.5.2. The results will be transferred to Actelion.

7.1.12 Sub-studies

7.1.12.1 Metabolism sub-study

^{18}F-FDG PET-MR scan will be performed according to the guidelines detailed in the **PET-MR image acquisition protocol**. The ^{18}F-FDG PET-MR scan of the sub-study will be combined with the cardiac MRI of the main study.

Complete results will be blinded to the patient identity and to the date of image acquisition prior to the assessment. The following variables will be centrally assessed according to a dedicated charter and the results will be sent to Actelion:

- RV ^{18}F-FDG uptake
- Aortic ^{18}F-FDG uptake
- Right common carotid ^{18}F-FDG uptake
- Left common carotid ^{18}F-FDG uptake

During the course of the PET-MR procedure, a blood sample will be taken (see **PET-MR image acquisition protocol**) and sent to the central laboratory which will assess the following variables and transfer the results to Actelion:

- Glucose
- Insulin
- Free fatty acid

7.1.12.2 Biopsy sub-study

During each RHC, a maximum of 4 biopsy samples will be withdrawn. Patients participating in the biopsy sub-study will also have additional blood samples taken at the same time points. Samples will be sent to the central laboratory which will coordinate the assessment of the following variables and transfer the results to Actelion:

Biopsies

- Immunochemistry: qualitative description of the samples after staining for:
  - Fibrosis
  - VEGF B
  - PCNA
  - Cleaved caspase 3
  - LC3B2
  - Caveolin

  - E NOS
  - NOX-2
- Relative quantitative assessment of selected proteins in biopsies, determined by Reverse Phase Protein Array[2]
- Determination by electron/light microscopy of:
  - Number of capillaries per cardiomyocyte
  - Mean cardiomyocyte volume
  - Description of cardiomyocytes and mitochondria
- Endomyocardium cells mRNA transcript analysis

Blood

- PBMC mRNA transcript analysis

7.1.12.3 Echo sub-study

Echo (i.e., 3D, 2D, M-mode and Doppler echocardiography) will be performed according to the guidelines detailed in the **Echo image acquisition protocol**. Complete results will be blinded to the patient identity and to the date of image acquisition. The following variables will be centrally assessed according to a dedicated charter and the results will be sent to Actelion:

- LV eccentricity index at end-diastole
- LV eccentricity index at end-systole
- Minimum diameter of the inferior vena cava (at inspiration)
- Maximum diameter of the inferior vena cava (at end-expiration)
- Tricuspid annular plane systolic excursion (TAPSE)
- Pericardial effusion size scored from 0 to 4
- Right ventricle acceleration time, by tissue Doppler and pulsed wave Doppler
- Right ventricle ejection time, by tissue Doppler and pulsed wave Doppler
- Total RV Systolic Time (duration of tricuspid insufficiency jet)
- Doppler RV index (RV myocardial performance index), by tissue Doppler and pulsed wave Doppler
- Tricuspid peak jet velocity
- RV systolic pressure (estimated by tricuspid valve Doppler)
- Early diastolic velocity of the jet of pulmonary valve regurgitation
- End-diastolic velocity of the jet of pulmonary valve regurgitation

[2] Akt - phosphor, AMPK alpha - phospho, Caspase-1, Caspase 3 - cleaved, Caveolin-1, c-Kit, CREB, CREB - phospho, Dihydropyrimidine dehydrogenase, DPYD, Erk1/2 - phospho, FAK1 - phospho, FAK1 - phospho, GDF-15, IGF1R, KLF-5, mTOR, mTOR - phospho, NF-kappaB p65, Nrf2, p53, PARP, PARP - cleaved, PCNA, PTEN, Raptor, STAT 3, STAT 3 - phospho, Superoxide dismutase (Cu/Zn).

- Cardiac output determined from LV outflow tract
- Mitral E-wave velocity
- Mitral A-wave velocity
- Mitral annulus peak early diastolic velocity E'
- E/A ratio
- E/E' ratio
- 2D RV dimension end-diastole
- Tricuspid peak annular velocity s'
- RV end diastolic area
- RV end systolic area
- RV fractional area change
- RVSV determined from pulmonary valve Doppler and pulmonary annulus dimension
- Tricuspid peak E, peak A, deceleration time
- Tricuspid peak diastolic annular velocities e', a'
- LVEDV determined from 2D measurements
- LVESV determined from 2D measurements
- Mitral deceleration time
- Mitral annular plane tissue Doppler velocity a'
- 2D Global Longitudinal RV strain
- 2D circumferential RV strain
- Time to peak RV strain
- RVSV
- RVEDV
- RVESV
- RVEF
- RV mass
- LVSV
- LVEDV
- LVESV
- LVEF
- LV mass
- RVEDV/LVEDV
- RVESV/LVESV

7.2 Efficacy assessments

7.2.1 6-minute walk test

The 6MWT will be evaluated as described in Section 7.1.6 during screening, at Week 26 and at Week 52. 6MWT will also be performed at RTI visit or premature EOT visit where applicable. 6MWT may be performed at other unscheduled visits if clinically indicated.

7.2.2 WHO Functional Class

WHO FC will be assessed as described in Section 7.1.7 during screening, at Week 26 and at Week 52. WHO FC will also be assessed at RTI visit or premature EOT visit where applicable. WHO FC may be assessed at other unscheduled visits if clinically indicated.

7.2.3 Cardiac MRI

Cardiac MRI will be performed as described in Section 7.1.8 during screening, at Week 26, and at Week 52.

In case of rescue therapy initiation or premature end of treatment (where applicable), cardiac MRI will be conducted depending on the visit date [Table 1] and will replace the Week 26 or Week 52 cardiac MRI.

7.2.4 Hemodynamics

RHC will be performed as described in Section 7.1.9 during screening and at Week 26.

In case of rescue therapy initiation or premature end of treatment before Week 26 (where applicable), RHC will be conducted depending on the visit date [Table 1] and will replace the Week 26 RHC.

7.2.5 Pressure-volume relationship

Pressure-volume relationship will be assessed as described in Section 7.1.10 based on cardiac MRI and RHC assessments performed during screening and at Week 26.

In case of rescue therapy initiation or premature end of treatment before Week 26 (where applicable), pressure-volume relationship will be assessed at the corresponding time point, provided RHC and cardiac MRI results are available for this time point.

7.2.6 Laboratory tests

Exploratory efficacy laboratory assessments [Section 7.3.5.2] will be done on blood samples collected during screening, at Week 26 and at Week 52. They will also be assessed at RTI visit or premature EOT visit where applicable.

7.3 Safety assessments

7.3.1 Adverse events

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

7.3.2 Vital signs

Vital signs will be assessed during screening, at Treatment Initiation Visit, at Week 26, and at EOT. They will also be assessed at RTI visit or premature EOT visit where applicable. Vital signs may be assessed at other unscheduled visits if clinically indicated.

Systolic and diastolic blood pressure and HR will be measured non-invasively in the supine position throughout the study.

7.3.3 Weight

Body weight (in underwear) will be measured during screening, at Week 26 and at Week 52. Weight will also be measured at RTI visit or premature EOT visit where applicable. Weight may be assessed at other unscheduled visits if clinically indicated.

Weight will be used in the calculation of BMI and of hemodynamic indices.

7.3.4 Physical examination

Physical examination (i.e., inspection, percussion, palpation and auscultation) will be performed during screening, at Treatment Initiation Visit, at Week 26 and at EOT. It will also be performed at RTI visit or premature EOT visit where applicable. Physical exam may be performed at other unscheduled visits if clinically indicated.

The observations must be reported according to body system in the CRF as either normal or abnormal. If an abnormality is found it must be specified on the corresponding CRF page, describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings (other than those related to PAH that were present at the time of informed consent signature) must be recorded on the Medical History CRF page. Physical examination findings made after study start, that meet the definition of an AE [Section 10.1.1] must be recorded by the investigator on the AE page of the CRF.

7.3.5 Laboratory assessments

7.3.5.1 Type of laboratory

A central laboratory (Covance; 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 automatically transferred from the central laboratory database to Actelion's clinical database.

During screening, patient eligibility may be determined using local laboratory tests as long as the central laboratory kit is used in parallel.

Under specific circumstances (e.g., if the patient lives distant from the site and cannot return every month), laboratory samples may be collected at a laboratory close to where the patient lives (satellite laboratory), and sent to the central laboratory for analysis. In such a case, the satellite laboratory 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 enrollment of the patient in the study. The supervision of the satellite laboratory remains under the responsibility of the principal investigator.

In exceptional cases (e.g., patient is hospitalized in a different hospital from the study center due to a medical emergency, missing laboratory values) the local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated CRF pages. If applicable, the investigator/delegate will provide Actelion with the name, professional degree, and *curriculum vitae* of the director of the satellite laboratory, a copy of the laboratory's certification, and the normal ranges for each laboratory test that is evaluated in the study. These laboratory references must be updated whenever necessary.

In case a central laboratory sample is lost or cannot be analyzed for any reason, the investigator will collect an additional sample as soon as possible for repeat 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 investigator. In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion and the concerned site. Alert flags that will trigger such notifications are displayed in Appendix 6.

All laboratory reports must be signed and dated by the principal 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 informed consent signature must be recorded on the medical history page of the CRF. Any clinically relevant laboratory abnormalities detected after informed consent signature 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 must be performed as 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.

7.3.5.2 Laboratory tests

Complete laboratory tests (hematology, clinical chemistry, coagulation tests, pregnancy test, and exploratory efficacy) will be performed during screening, at Week 26 and at Week 52. These tests will also be performed at RTI visit or premature EOT visit where applicable.

Monthly LFT and hemoglobin monitoring are mandatory during the first 6 months of study drug treatment. Patients must be monitored for signs of hepatic injury, and monthly LFT monitoring is recommended beyond the first 6 months of study treatment.

All laboratory tests results will be transferred from the central laboratory to the clinical database.

Pregnancy tests will be performed for women of childbearing potential at Treatment Initiation Visit, monthly until end of study treatment, at EOS, and if pregnancy is suspected during the study.

Negative urine pregnancy test results will not be entered in the CRF.

<u>Hematology</u>

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

<u>Clinical chemistry</u>

- LFT: Aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, LDH
- Creatinine, urea
- Uric acid
- Glucose
- Cholesterol, triglycerides
- Sodium, potassium, chloride, calcium
- Protein, albumin

<u>Coagulation tests</u>

- Prothrombin time and/or International Normalized Ratio (INR)
- Activated partial thromboplastin time (aPTT)

Pregnancy test for women of childbearing potential

Serum pregnancy tests will be performed at each blood draw (during screening, at Week 26 Visit, at EOT, at RTI visit or premature EOT visit where applicable) and if pregnancy is suspected during the study.

Urine pregnancy tests will be performed at Treatment Initiation Visit and at EOS.

Monthly pregnancy tests will be performed using the monthly blood draws where applicable, and with urine pregnancy tests otherwise.

Urine pregnancy test kits will be provided by the central laboratory or the contract research organization (CRO).

Pregnancy reporting requirements are described in Section 10.3.

Efficacy / Exploratory

- NT-proBNP
- Uric acid
- Red cell distribution width
- Activin A
- Cystatin C
- Follistatin
- Galectin-3
- GDF-15
- Cardiac troponin T
- LDH
- Osteoprotegerin
- TNF alpha
- Potential additional laboratory tests [see Section 7.3.5.3].

7.3.5.3 Potential additional laboratory tests

The list of biomarkers in this protocol may be expanded with additional circulating biomarkers reflecting cardiac remodeling or function based on available scientific evidence. No genetic testing will be performed. The samples will be stored at the central laboratory until one year after the last patient's last visit and destroyed after that date.

7.4 Exploratory assessments in sub-studies

These assessments are carried out only in patients enrolling in the respective sub-study.

7.4.1 Metabolism sub-study

^{18}F-FDG PET-MR scan will be performed as described in Section 7.1.12.1 during screening, at Week 26 and at Week 52.

In case of rescue therapy initiation or premature end of treatment (where applicable), ^{18}F-FDG PET-MR scan will be conducted depending on the visit date [Table 1] and will replace the Week 26 or Week 52 ^{18}F-FDG PET-MR scan.

7.4.2 Biopsy sub-study

Biopsies will be taken during the RHC procedure as described in Section 7.1.12.2 and an additional blood sample will be taken. Biopsy and blood draw will be conducted during screening and at Week 26. If a RHC is performed at RTI or premature EOT, biopsies and an additional blood sample will be taken at that time and will replace the Week 26 biopsy.

7.4.3 Echo sub-study

Echo will be performed as described in Section 7.1.12.3 during screening, at Week 26 and at Week 52.

In case of rescue therapy initiation or premature end of treatment (where applicable), Echo will be conducted and will replace the Week 26 or Week 52 Echo.

8 SCHEDULE OF VISITS

To ensure compliance, at each visit the study personnel must remind women of childbearing potential to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

It is permitted to re-screen patients once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication, etc.), provided that documented authorization has been received from Actelion. All screening assessments must then be repeated at the time of re-screening.

For a tabulated summary of all visits and assessments described in the following sections see Table 1.

8.1 Screening period

Assessments of the screening period must be performed within 28 days prior to Treatment Initiation Visit (Day 1). It is the responsibility of the investigator to obtain written informed consent from each patient participating in the study after adequate explanation of the objectives, methods and potential hazards of the study.

The ICF must be signed and dated by both parties prior to any study assessment or procedure at the latest.

The screening period includes [see Table 1]:

- Eligibility criteria check
- Recording of demographic and baseline characteristics
- Recording of medical history
- Weight
- Recording of previous and concomitant medications
- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs
- 6MWT
- WHO FC
- Cardiac MRI
- RHC (provided that the above mentioned criteria are compatible with study eligibility criteria)
- Blood tests
- Recording of AEs and SAEs

Cardiac MRI and RHC must be conducted within 21 days of each other.

For patients enrolling in the corresponding sub-study only, the following assessments/procedures must also be conducted during the screening period:

- PET-MR scan with injection of ^{18}F-FDG (combined with cardiac MRI)
- Endomyocardium biopsy and additional blood sample
- Echo

8.2 Treatment period

8.2.1 Treatment Initiation Visit

Treatment Initiation Visit may occur on the day of the last screening assessment, provided that all assessments are done before study drug intake.

Treatment Initiation Visit includes:

- Recording of concomitant medications
- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs
- Urine pregnancy test for women of childbearing potential
- First intake of study drug
- Recording of AEs and SAEs

8.2.2 Rescue Therapy Initiation Visit

In case of disease progression that requires initiation of rescue therapy before Week 26 RHC, a site visit is organized and the following assessments are to be performed before the actual rescue therapy initiation:

- Weight
- Recording of concomitant medications
- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs
- 6MWT
- WHO FC
- Cardiac MRI
  - Before Week 16: decision to conduct the exam based on clinical judgment
  - Between Week 16 and Week 26 RHC: must be performed and replaces Week 26 cardiac MRI
- RHC
  - Before Week 16: decision to conduct the exam based on clinical judgment
  - Between Week 16 and Week 26 RHC: must be performed and replaces Week 26 RHC
- Blood tests
- Recording of AEs and SAEs

Cardiac MRI and RHC must be conducted within 21 days of each other.

For patients in the corresponding sub-study only, the following assessments/procedures are also conducted:

- PET-MR scan with injection of ^{18}F-FDG (combined with cardiac MRI), replaces Week 26 ^{18}F-FDG PET-MR scan
- Endomyocardium biopsy and additional blood sample if a RHC is performed. This replaces Week 26 biopsy and blood sample
- Echo, replaces Week 26 Echo

For patients with multiple opportunities to undergo cardiac MRI, RHC, PET-MR scan, biopsy and Echo in replacement of Week 26 (e.g., several RTI before Week 26 RHC or RTI and EOT before Week 26 RHC), these exams are done once only.

8.2.3 Week 26 visit

At Week 26 (± 14 days), the following assessments will be performed:

- Weight
- Recording of concomitant medications

- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs
- 6MWT
- WHO FC
- Cardiac MRI
- RHC
- Blood tests
- Recording of AEs and SAEs

Cardiac MRI and RHC must be conducted within 21 days of each other.

For patients in the corresponding sub-study only:

- PET-MR scan with injection of ^{18}F-FDG (combined with cardiac MRI)
- Endomyocardium biopsy and additional blood sample
- Echo

8.2.4 Unscheduled visits

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

Assessments performed may include:

- Weight if clinically indicated
- Recording of concomitant medications
- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs if clinically indicated
- 6MWT if clinically indicated
- WHO FC if clinically indicated
- Recording of AEs and SAEs

Decreases in 6MWD > 15% from baseline in conjunction with worsening WHO FC that occur between scheduled visits and do not result in an RTI visit must be recorded in the eCRF using an unscheduled visit form.

8.2.5 Premature End of Treatment visit

8.2.5.1 Patients discontinuing the study

The reason for premature discontinuation from the study and the person making the decision will be collected [see Section 9.2]. The investigator must seek and document agreement to conduct the safety follow-up.

For patients enrolled in a sub-study, the investigator must clarify whether the patient wants to discontinue the sub-study only, or both the main study and the sub-study.

8.2.5.2 Patients agreeing to limited participation

For patients permanently discontinuing study treatment who accept to continue study assessments [see Section 9.2], the premature EOT visit takes place at the latest 7 days after the decision to end study treatment and includes:

- Reason for premature discontinuation and person taking the decision
- Weight
- Recording of concomitant medications
- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs
- 6MWT
- WHO FC
- Cardiac MRI
  - Before Week 16: decision to conduct the exam based on clinical judgment
  - Between Week 16 and Week 26 RHC: must be performed and replaces Week 26 cardiac MRI
  - Between Week 26 RHC and Week 48: decision to conduct the exam based on clinical judgment
  - After Week 48: must be performed and replaces Week 52 cardiac MRI
- RHC
  - Before Week 16: decision to conduct the exam based on clinical judgment
  - Between Week 16 and Week 26 RHC: must be performed and replaces Week 26 RHC
- Blood tests
- Recording of AEs and SAEs

Cardiac MRI and RHC must be conducted within 21 days of each other.

For patients in the corresponding sub-study only, the following assessments/procedures are also conducted:

- PET-MR scan with injection of ^{18}F-FDG (combined with cardiac MRI)

- Before Week 26 RHC: must be performed and replaces Week 26 ^{18}F-FDG PET-MR scan
- Between Week 26 RHC and Week 48: must be performed and replaces Week 52 ^{18}F-FDG PET-MR scan

- Endomyocardium biopsy and additional blood sample if a RHC is performed. This replaces Week 26 biopsy and blood sample
- Echo
  - Before Week 26 RHC: must be performed and replaces Week 26 Echo
  - Between Week 26 RHC and Week 48: must be performed and replaces Week 52 Echo

For patients with multiple opportunities to undergo cardiac MRI, RHC, PET-MR scan, biopsy and Echo in replacement of Week 26 (e.g., several RTI before Week 26 RHC or RTI and EOT before Week 26 RHC), these exams are done once only.

Premature EOT visit is followed by the safety follow-up, 30 to 37 days after study treatment discontinuation.

8.2.6 End of Treatment visit

At Week 52 (± 7 days), the following assessments will be repeated:

- Weight
- Recording of concomitant medications
- Recording of birth control methods for women of childbearing potential
- Physical examination and vital signs
- 6MWT
- WHO FC
- Cardiac MRI
- Blood tests
- Recording of AEs and SAEs

For patients in the corresponding sub-study only:

- PET-MR scan with ^{18}F-FDG (combined with cardiac MRI)
- Echo

8.3 Safety follow-up

EOS visit

The EOS visit occurs 30 to 37 days after study drug discontinuation. Agreement to conduct the safety follow-up must have been sought for patients who withdrew their consent. The visit can be done via telephone, and includes:

- Recording of concomitant medications.
- Urine pregnancy test for women of childbearing potential.
- Recording of birth control methods for women of childbearing potential.
- Recording of AEs and SAEs.

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

Sites will be informed once planned enrollment is met for the study and the sub-studies, or if enrollment is stopped early following interim analysis results. Patients in screening will be allowed to continue in the study. No additional patient can be screened after enrollment closure.

For an individual patient, study is completed at the EOS Visit.

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

9.2 Premature withdrawal from study

Patients may voluntarily withdraw from the study for any reason at any time. Patients are considered withdrawn if:

- They state an intention to withdraw further participation in all components of the study.
- They die.
- They are lost to follow-up for any other reason (see below).
- The investigator believes that continued participation in the study would be contrary to the best interests of the patient.
- Actelion makes this decision for any reason, including premature termination or suspension of the study [see Section 9.3].

Patients are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the patient fail. The site must take preventive measures to avoid a patient being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, e-mail address, person to be contacted in case the patient cannot be reached). If the patient cannot be reached, the site must make a reasonable effort to contact the patient, document all attempts and enter the loss of follow-up information into the CRF. 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

patient's home), respecting the patient's right to privacy. If the patient is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

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

If for any reason (except death or loss-to-follow-up) a patient is withdrawn from the study, the investigator must make efforts to conduct a last visit to assess the safety and well-being of the patient, collect unused study drug and discuss follow-up medical care. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

9.3 Premature termination or suspension of the study

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

If a study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the Institutional Review Boards or Independent Ethics Committees (IRBs/IECs) and Health Authorities, as appropriate, and provide the reasons for the suspension or termination.

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

In addition, if the investigator suspends or terminates 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 Steering Committee.

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

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

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 patient during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until EOS, which is 30 to 37 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs:

- 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.
- 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 must be reported as an AE and, in addition, study treatment errors must be documented in the study drug log of the CRF.

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 CRF.

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

The three categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

A mild, moderate, or severe AE may or may not be serious [see Section 10.3.1]. These terms are used to describe the intensity of a specific event. Medical judgment must 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 treatment, and reported as either related or unrelated. The determination of the likelihood that the study drug caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated with 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. Examples include discontinuation of a patient's previous treatment during a washout period leading to exacerbation of underlying disease.

10.1.5 Reporting of adverse events

All AEs occurring after informed consent signature and up to EOS, which is 30 to 37 days after study treatment discontinuation must be recorded on specific AE pages of the CRF.

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 International Council for Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring 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 patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to informed consent signature) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- However, complications that occur during hospitalization are AEs or SAEs (for example, if a complication prolongs hospitalization).

10.2.1.2 Serious adverse events associated with the study design or protocol mandated procedures

An SAE 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. Examples include discontinuation of a patient's previous treatment during a washout period leading to exacerbation of underlying disease, or a complication of an invasive procedure that is specifically required by the protocol.

10.2.2 Reporting of serious adverse events

10.2.2.1 During screening period

All SAEs that occur after informed consent signature must be reported.

These SAEs must be reported on an SAE form and on the AE pages in the CRF.

10.2.2.2 During treatment period

All SAEs, regardless of investigator-attributed causal relationship, must be reported.

These SAEs must be reported on an SAE form and on the AE pages in the CRF.

10.2.2.3 During follow-up period

All SAEs which occur up to 30 days after study treatment discontinuation must be reported.

These SAEs must be reported on an SAE form and on the AE pages in the CRF.

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-day follow-up period must be reported to the Actelion drug safety department within 24 h of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study treatment or study design or protocol-mandated procedures by the investigator.

10.2.5 Reporting procedures

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

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

The SAE forms must be faxed or emailed 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 h of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

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

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to Health Authorities, ECs/IRBs and investigators is the reference safety information section of the IB.

The SAEs listed below are commonly seen with the underlying disease and are therefore expected to occur in this patient population. These SAEs must be reported on an SAE form and on the CRF. These SAEs do not require systematic expedited reporting to Health Authorities, IRBs/IECs, and investigators.

The following events that are expected to occur in patients with PH or PAH will be considered as 'disease-related' and 'expected' for regulatory reporting purposes in this population: signs and symptoms of PAH/PH, worsening/exacerbation/progression including fatal outcome, and, in particular, abdominal pain, anorexia, chest pain, cyanosis, diaphoresis, dizziness, pre-syncope, dyspnea, orthopnea, fatigue, hemoptysis, heart failure, hypoxia, palpitations, syncope, collapse, systemic arterial hypotension, and tachycardia.

10.3 Pregnancy

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

10.3.1 Reporting of pregnancy

Any pregnancy occurring from treatment initiation until the end of the 30 days safety follow-up must be reported within 24 h of the investigator's knowledge of the event.

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

10.3.2 Follow-up of pregnancy

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

Any AE associated with the pregnancy occurring during the follow-up period after study drug discontinuation must be reported on separate AE pages in the CRF. 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) is monitored and reviewed on a continuous basis by the Actelion clinical team (in charge of ensuring patients' safety as well as data quality) by periodically monitoring clinical studies activities from protocol conception to database closure.

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CROs 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 Patients Set

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

11.1.2 Safety Set

The Safety Set (SS) includes all patients from the Screened Patients Set who received at least one dose of study drug.

11.1.3 Full Analysis Set

The Full Analysis Set (FAS) includes all patients from the SS who had a baseline as well as a post-baseline measurement for both primary endpoints (RVSV and PVR).

The Modified FAS comprises all patients included in the FAS who had a post-baseline measurement *taken between 16 weeks and 30 weeks of treatment* for both primary endpoints.

11.1.4 Per Protocol Set

The Per Protocol Set (PPS) comprises all patients included in the Modified FAS without major protocol deviations that affect the main analysis of the primary efficacy variables. The reasons for excluding patients from the PPS will be fully defined and documented in the SAP.

11.1.5 Other analysis sets

The specific RVSV Analysis Set includes all patients from the SS who had a baseline as well as a post-baseline measurement *taken between 16 weeks and 30 weeks of treatment* for RVSV.

The specific PVR Analysis Set includes all patients from the SS who had a baseline as well as a post-baseline measurement *taken between 16 weeks and 30 weeks of treatment* for PVR.

Specific analysis sets for the sub-studies will be defined in the SAP.

11.1.6 Usage of the analysis sets

The primary efficacy analysis will be performed on the Modified FAS. Secondary and exploratory efficacy analyses will be performed on the FAS.

The PPS will be used for performing a sensitivity analysis on the primary endpoints.

The specific RVSV and PVR Analysis Sets will only be used if the intersection of the two sets (i.e., the Modified FAS) is markedly smaller than the union. Criteria will be specified in the SAP.

Safety analyses will be performed on the SS. Patient listings will be based on the Screened Patients Set, unless otherwise specified.

Patient disposition will be described for the Screened Patients Set.

11.2 Variables

11.2.1 Primary efficacy variables

The two primary efficacy variables are:

- Change from baseline to Week 26 in RVSV assessed by cardiac MRI from pulmonary artery flow.
- Ratio of Week 26 to baseline PVR assessed by RHC.

Change from baseline in RVSV (mL) is calculated as RVSV at Week 26 minus RVSV at baseline. A positive change from baseline corresponds to an improvement.

PVR [dyn·s·cm^{-5}] is calculated as (mPAP − PCWP) / CO × 80 [refer to Appendix 1]. A ratio versus baseline < 1 corresponds to an improvement.

11.2.2 Secondary efficacy variables

Secondary efficacy variables are absolute changes from baseline to Week 26 in:

- RVEDV (mL)
- RVESV (mL)
- RVEF (%)
- RV mass (g)
- 6MWD (m)
- WHO FC (I–IV)

11.2.3 Exploratory efficacy variables

11.2.3.1 Hemodynamic variables and pressure-volume variables

These variables include changes from baseline to Week 26 in:

- mPAP (mmHg)
- mRAP (mmHg)
- Cardiac index (L/min/m^2)
- Arterial elastance (mmHg/mL)
- RV end-systolic elastance (mmHg/mL)
- RV maximum isovolumic pressure (mmHg)

11.2.3.2 Variables related to maintenance of treatment effect

These variables include changes from baseline to Week 52 for the primary and secondary efficacy variables (except those determined by RHC which is not performed at Week 52):

- RVSV determined by cardiac MRI from pulmonary artery flow
- RVEDV
- RVESV
- RVEF
- RV mass
- 6MWD
- WHO FC

11.2.3.3 Variables related to the left ventricle

These variables include changes from baseline to Week 26 and Week 52 in:

- LVSV determined by cardiac MRI from the aortic flow (mL)
- LVEDV (mL)
- LVESV (mL)

- LVEF (%)
- LV mass (g)
- RVEDV/LVEDV (1)
- RVESV/LVESV (1)

11.2.3.4 Potential variables for disease monitoring

These endpoints include changes from baseline to Week 26 and Week 52 in:

- NT-proBNP
- Uric acid
- Red cell distribution width
- Activin A
- Cystatin C
- Follistatin
- Galectin-3
- GDF-15
- Cardiac troponin T
- LDH
- Osteoprotegerin
- TNF alpha

11.2.3.5 Clinical endpoint

The clinical endpoint is the time from the initiation of treatment to first clinical worsening defined as the first occurrence of:

- Decrease in 6MWD by > 15% from baseline associated with worsening in WHO FC, *or*
- Initiation of s.c. or i.v. prostanoid therapy, *or*
- Hospitalization for PAH (investigator's assessment), *or*
- Death

11.2.4 Safety variables

Safety variables include:

- Treatment-emergent AEs up to 30 days after EOT
- Treatment-emergent SAEs up to 30 days after EOT
- AEs leading to premature discontinuation of study drug
- Treatment-emergent marked laboratory abnormalities up to 30 days after EOT
- Occurrence of LFT (ALT or AST) abnormalities up to EOT, classified as:
  - $\geq 3 \times$ ULN
  - $\geq 3 \times$ ULN and $< 5 \times$ ULN

- ≥ 5 × ULN and < 8 × ULN
- ≥ 8 × ULN

- Occurrence of hemoglobin abnormalities up to EOT, classified as:
  - ≤ 80 g/L
  - > 80 g/L and ≤ 100 g/L
- Occurrence of ALT and/or AST abnormality ≥ 3 × ULN associated with bilirubin ≥ 2 × ULN

11.2.5 Other variables

Variables associated with the sub-studies will be described in the SAP.

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

The overall type I error is α = 0.025 (one-sided) and will be split between the two primary endpoints RVSV (α = 0.02) and PVR (α = 0.005). The justification for the unequal split is that PVR is a well-known endpoint (hence, the smaller part of the α), whereas RVSV is less well-known, i.e., more uncertainty of the estimate/variability (hence, the larger part of the α).

Per endpoint the type II error is set to 0.10 and the power to 90%.

An efficacy interim analysis is introduced in protocol Version 6 and corresponding statistical considerations are provided in Section 11.4.3.

11.3.2 Analysis of the primary efficacy variables

11.3.2.1 Hypotheses and statistical model

The null hypothesis is:

The mean change from baseline to Week 26 in RVSV is less than or equal to zero AND the geometric mean ratio of Week 26 to baseline PVR is greater than or equal to one.

The alternative hypothesis is:

The mean change from baseline in RVSV is greater than zero OR the geometric mean ratio of Week 26 to baseline PVR is less than one.

11.3.2.2 Handling of missing data

General. RVSV will be based on pulmonary artery flow. If, however, RVSV determined from pulmonary artery flow differs from RVSV determined from aortic flow by more than 20% (in either direction), then RVSV should be determined by volumetric assessment.

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

1. If PCWP is missing both at baseline and post-baseline, the study population median PCWP (baseline and post-baseline, respectively) will be imputed (based on the Modified FAS).
2. If PCWP is missing either at baseline or post-baseline, the patient's available PCWP will be imputed.

This imputation is based on the clinical assumption that macitentan does not affect PCWP.

Baseline. Patients without a baseline RVSV or PVR measurement will be excluded from the analyses.

Post-baseline. In patients without a Week 26 RVSV or PVR the last post-baseline measurement (presumably taken at treatment discontinuation or initiation of rescue therapy) will be carried forward, provided that this measurement was taken after at least 16 weeks of treatment. Week 26 measurements taken after 30 weeks of treatment will be excluded from the analyses.

11.3.2.3 Main analysis

The primary efficacy analysis will be performed on the Modified FAS for the interim and the final analysis.

RVSV will be summarized by time point (baseline, Week 26) using descriptive statistics (n, mean, SD, median, Q1 and Q3). The change from baseline to Week 26 in RVSV will be summarized similarly.

Change from baseline in RVSV will be analyzed using an Analysis of Covariance (ANCOVA) with a factor for other PAH-specific therapy (none, background or initiated at baseline) and a covariate for baseline RVSV. The mean change from baseline and its **96%** confidence interval (CI) will be estimated based on the model.

PVR will be summarized by time point using descriptive statistics as well as geometric means and Coefficients of Variation (CVs). The Week 26 versus baseline ratio in PVR will be summarized similarly.

The ratio of Week 26 versus baseline PVR will be log-transformed (base e) and analyzed using an ANCOVA with a factor for other PAH-specific therapy (none, background or initiated at baseline) and a covariate for baseline log PVR. The mean change from baseline (on log scale) and its 99% CI will be estimated based on the model. The geometric mean ratio (versus baseline) and its 99% CI will be obtained by exponentiation.

The log transformation for PVR is justified by the fact that ratios versus baseline follow a normal distribution more closely after a log transformation. In addition, mean absolute changes from baseline on log scale can be translated into (geometric) mean ratios by exponentiation.

The null hypothesis will be tested at interim and final analysis, if study continues, and may be rejected based on pre-defined boundaries defined in Section 11.4.3.

11.3.2.4 Supportive/sensitivity analyses

A sensitivity analysis will be performed on the FAS. In patients without a Week 26 RVSV or PVR the last post-baseline measurement will be carried forward, regardless of the time it was taken. Week 26 measurements performed after 30 weeks of treatment will be excluded from the analysis.

Another sensitivity analysis will be performed on the PPS that will (at least) be restricted to completers, i.e., patients with Week 26 RVSV and PVR measurements taken between 22 and 30 weeks of treatment.

A sensitivity analysis will also be performed on the SS that may include patients without post-baseline RVSV or PVR. For those patients, the Week 26 RVSV or PVR measurement needs to be imputed. Imputation rules will be specified in the SAP.

Sensitivity analyses for RVSV and PVR may also be performed for the specific RVSV and PVR Analysis Sets, respectively, but only if deemed necessary as specified in the SAP.

11.3.2.5 Subgroup analyses

Subgroup analyses for the primary endpoints will be performed only at final analysis for patients with versus without PAH-specific therapy at baseline using the ANCOVA models specified in Section 11.3.2.3, but without the factor for PAH-specific therapy. In this analysis 95% CIs will be used.

Subgroup analyses for RVSV and log PVR will also be performed for patients on WHO FC I–II versus III using the ANCOVA models specified in Section 11.3.2.3, In this analysis 95% CIs will be used.

Additional subgroup analyses will be specified in the SAP.

Exploratory analyses will be performed aimed at identifying prognostic factors for changes from baseline in RVSV and log PVR. This will be done using linear regression models. Candidate prognostic factors will be specified in the SAP.

11.3.3 Analysis of the secondary efficacy variables

Secondary efficacy analyses will be performed only at final analysis on the Modified FAS at $\alpha = 0.025$ (one-sided) using 95% CIs. Supportive secondary efficacy analyses will also be performed on the FAS. No correction for multiple testing will be applied for these analyses.

MRI-based secondary efficacy variables (changes from baseline to Week 26 in RVEDV, RVESV, RVEF, RV mass) will be summarized and analyzed as described for RVSV in Section 11.3.2.3.

The 6MWD will be summarized by time point using descriptive statistics. Change from baseline to Week 26 will be summarized similarly. Change from baseline in 6MWD will be analyzed using an ANCOVA with a factor for other PAH-specific therapy (none, background or initiated at baseline) and a covariate for baseline 6MWD and WHO FC.

WHO FC will be summarized by time point using frequency tables. Changes from baseline in WHO FC will be dichotomized as worsening (i.e., change > 0) versus no change or improvement (i.e., change ≤ 0). Worsening will be analyzed using a logistic regression model with a factor for background PAH-specific therapy at baseline.

NT-proBNP will be summarized by time point using descriptive statistics as well as geometric means and CVs. The Week 26 versus baseline ratio will be summarized similarly. The ratio versus baseline in NT-proBNP will be log-transformed and analyzed using an ANCOVA with a factor for other PAH-specific therapy (none, background or initiated at baseline) and a covariate for baseline log NT-proBNP.

11.3.4 Analysis of the exploratory efficacy variables

Other efficacy variables will be summarized for the Modified FAS using descriptive statistics only. No statistical analyses will be performed.

Hemodynamic variables [Section 11.2.3.1] will be summarized by time point using descriptive statistics. Week 52 variables [Section 11.2.3.2] will be summarized similarly to the corresponding Week 26 measurements.

Pressure-volume variables (changes from baseline to Week 26 in arterial elastance, RV end-systolic elastance, RV maximum isovolumic pressure) will be summarized and analyzed as described for PVR in Section 11.3.2.3, but without the log-transformation.

Variables related to the left ventricle [Section 11.2.3.3] will be summarized similarly as the corresponding right ventricular variables. The ratios RVEDV/LVEDV and RVESV/LVESV will be summarized using descriptive statistics as well as geometric means and CVs. Potential variables for disease monitoring [Section 11.2.3.4] will be summarized similarly as NT-proBNP.

The clinical endpoint, time to first clinical worsening [Section 11.2.3.5] will be summarized using a Kaplan-Meier plot.

Association between (change from baseline to Week 26 in) cardiac MRI variables and time to first clinical worsening event will be explored using Cox models.

11.3.5 Analysis of safety variables

All safety analyses will be performed on the SS. All safety data will be listed, with flags for quantitative abnormalities.

11.3.5.1 Adverse events

A treatment-emergent AE is any AE temporally associated with the use of a study drug from study drug initiation until 30 days after study drug discontinuation.

The number and percentage of patients experiencing treatment emergent AEs and SAEs at least once from baseline up to 30 days following study drug discontinuation will be tabulated by:

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

Furthermore, treatment-emergent AEs and SAEs occurring up to 30 days after study drug discontinuation will be tabulated as described above by severity and relationship to study drug.

AEs leading to premature discontinuation of study drug and death will also 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 drug, and for AEs leading to death.

11.3.5.2 Laboratory parameters

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

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

Marked laboratory abnormalities will be summarized for each laboratory parameter by incidence and frequency. Absolute values and changes of laboratory parameter values during the course of the study from baseline up to EOT plus 30 days will be summarized using the usual location and scale summary statistics.

Laboratory parameters include:

- Hematology: hemoglobin, hematocrit, erythrocyte count (reticulocyte count), leukocyte count with differential counts, platelet count.
- Blood chemistry: AST, ALT, alkaline phosphatase, total and direct bilirubin, LDH, creatinine, urea, uric acid, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, protein, albumin.
- Coagulation tests: prothrombin time, INR, aPTT.

The number and percentage of patients with LFT abnormalities [classified as in Section 11.2.4] up to 30 days after study drug discontinuation will be tabulated.

The number and percentage of patients with hemoglobin abnormalities [classified as in Section 11.2.4] up to 30 days after study drug discontinuation will be tabulated.

11.3.5.3 Vital signs and body weight

Vital signs parameters blood pressure (i.e., diastolic blood pressure and systolic blood pressure), HR, and body weight will be summarized at each study visit up to EOT using the usual location and scale summary statistics for both absolute values and changes from baseline. Patients for whom no post-baseline value is available are excluded from the analysis of the changes from baseline in the SS.

11.3.6 Analysis of other variables

Analyses associated with the sub-studies will be described in the SAP.

11.4 Interim analyses

11.4.1 Rationale

The determination of the sample size necessary to conclude on RVSV at final analysis relied on assumptions derived from a single source [Section 11.5]. Therefore, a conservative approach was taken and led to a large sample size, i.e., 100 patients, to increase the probability of this study being conclusive.

Literature recently published [Hassoun 2015, Trip 2015, Brewis 2016] [Table 2] is in line with the initial assumptions, and suggests that the treatment effect on RVSV might be demonstrated before reaching 100 patients. Therefore, an interim analysis will be performed to allow for an early completion of the study for efficacy.

Table 2 New data published in 2015/2016

Reference	Patients with follow-up data	Reported data
[Hassoun 2015]	24 incident CTD-PAH patients treated with PDE-5 inhibitor–ERA combination for 36 weeks	Median (Q1-Q3) Baseline RVEDV (mL): 151.2 (138.4–177.4) Median (Q1-Q3) Post-treatment RVEDV (mL): 146.4 (120.5–165.4) Median (Q1-Q3) Baseline RVESV (mL): 82.1 (65.6–97.7) Median (Q1-Q3) Post-treatment RVESV (mL): 55.8 (49.4–79.2)
[Brewis 2016]	42 incident PAH patients mainly treated with PDE-5 inhibitor and/or ERA for 3–8 months	Mean (SD) Baseline Stroke volume index (mL/min2): 27 (8) Mean (SD) Post-treatment Stroke volume index (mL/m2): 32 (9)
[Trip 2015]	30 incident IPAH or HPAH patients treated with PAH therapies for 0.5–2.5 years	Median (Q1-Q3) Baseline RVEDV (mL): 140 (124–161) Median (Q1-Q3) Post-treatment RVEDV (mL): 137 (117–163) Median (Q1-Q3) Baseline RVESV (mL): 93 (72–109) Median (Q1-Q3) Post-treatment RVESV (mL): 73 (54–91)

CTD-PAH = Connective Tissue Disease - Pulmonary Arterial Hypertension; HPAH = Heritable Pulmonary Arterial Hypertension; IPAH = Idiopathic Pulmonary Arterial Hypertension; PAH = Pulmonary Arterial Hypertension; PDE-5 = Phosphodiesterase type 5; ERA = Endothelin Receptor Antagonist; RVEDV = Right Ventricular End Diastolic Volume; RVESV = Right Ventricular End Systolic Volume.

11.4.2 Conduct

An interim analysis will be conducted when the first 42 evaluable patients (i.e., included in the Modified FAS) are available for primary efficacy analysis.

The interim analysis will use a hierarchical testing approach to maintain the overall type I error. As a first step, change from baseline to Week 26 in RVSV will be tested. If the test is negative, i.e., the pre-defined efficacy boundary (p-value) is not crossed, recruitment will continue until 100 patients are enrolled. If it is positive (pre-defined efficacy boundary crossed), then PVR (ratio of Week 26 to baseline) will be tested.

RVSV is to be tested first, as the potential effects of PAH-specific therapy on this variable are not so well known. The effect of such therapies on PVR is better known with

robust treatment effect estimates, i.e., there is less uncertainty on the treatment effect estimate.

If the test on PVR is also positive, then the study will be declared positive for its primary endpoint. If the test on PVR is negative, no conclusion can be made with regards to the primary endpoint, and patient accrual will continue until 100 patients are enrolled.

To declare the study positive at the interim analysis, both endpoints must be met. This contrasts with the final analysis, where it is sufficient to meet one endpoint. The reason for this choice is to mitigate the risk of closing the study too early to observe the full potential of macitentan.

11.4.3 Statistical analysis

The interim analysis will be performed on the Modified FAS. Efficacy boundaries are defined in Table 3 and Table 4, and are calculated with 90% power, 1-sided 0.02 alpha for RVSV test, 1-sided 0.005 alpha for PVR test and are based on assumptions described in Section 11.5 (sample size). To accommodate the need for the same number of patients included in the interim analysis of each primary endpoint, the selected information fraction (around 50%) is slightly different for RVSV and PVR.

11.5 Sample size

For MRI-based RVSV, no individual patient data are available at Actelion. Individual RVSV was *approximated* in the hemodynamic sub-study of SERAPHIN (AC-055-302) combining the cardiac index obtained from the RHC with BSA and HR from vital signs measurements. The change from baseline in approximate RVSV was around 9 mL, in line with literature suggesting that a difference of 8–12 mL is clinically relevant [Van Wolferen 2011]. Assuming a standard deviation of 18–22 mL, also based on the hemodynamic sub-study of SERAPHIN, the sample size for 90% power is 30–93 evaluable patients for final analysis ($\alpha = 0.02$, one-sided). The number of patients and efficacy boundaries for the interim analysis are described in Table 3.

For PVR, an integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), and the hemodynamic sub-study of SERAPHIN suggested that the mean change from baseline is expected to be around −0.24 on log scale (95% CI: −0.29, −0.19) and that the within group standard deviation is around 0.41 on log scale (90% CI: 0.39, 0.43). Under these assumptions, 30–84 evaluable patients are needed for final analysis for 90% power ($\alpha = 0.005$, one-sided). The number of patients and efficacy boundaries for the interim analysis are described in Table 4.

The scenario retained to compute number of patients and p-value boundaries for interim/final analyses is based on conservative assumptions (lowest change and highest variability), and is described in Table 3 (RVSV) and Table 4 (PVR) below.

Table 3 Efficacy boundaries for RVSV endpoint at interim/final analyses

Change from baseline	SD	Information fraction for interim analysis	Number of patients needed at interim analysis	Number of patients needed at final analysis	Efficacy Boundary on p-value scale (Lan DeMets Pocock) – Interim analysis	Efficacy Boundary on p-value scale (Lan DeMets Pocock) – Final analysis
8	22	0.45	42	93	0.01149	0.01138

RVSV = Right Ventricular Stroke Volume; SD = Standard Deviation.

Table 4 Efficacy boundaries for PVR endpoint at interim/final analyses

Change from baseline on log scale	SD	Information fraction for interim analysis	Number of patients needed at interim analysis	Number of patients needed at final analysis	Efficacy Boundaries on p-value scale (LanDeMets Pocock) – Interim analysis*	Efficacy Boundaries on p-value scale (LanDeMets Pocock) – Final analysis**
−0.19	0.43	0.5	42	84	0.0031	0.00247

* Test at interim only if RVSV crossed pre-defined efficacy boundary. The information fraction for PVR is higher than for RVSV to fit same number of patients at interim analysis for both endpoints.

** Boundary is 0.005 if not tested at interim

PVR = Pulmonary Vascular Resistance; RVSV = Right Ventricular Stroke Volume; SD = Standard Deviation.

To account for patient dropout and non-evaluable images, the sample size was set at 100 patients for the final analysis.

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 must be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the electronic CRF derived from source documents must be consistent with the source documents.

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 (ref. to 21 CFR Part 11).

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

For each patient screened, regardless of study treatment initiation, a CRF must be completed and signed by the investigator/delegate. This also applies to those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF.

12.2 Maintenance of data confidentiality

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

12.3 Database management and quality control

Electronic CRFs will be used for all patients. Investigators will have full access to the site CRF data until the database is locked. Thereafter, they will have read-only access. The CRF must be kept current to reflect patient status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion 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 CRF. 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 CRF, or simply a data correction in the CRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of Health Authority queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected. This process will continue until database closure.

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

Cardiac MRI, PET-MR, Echo and biopsies will be centrally assessed and the results will be sent electronically to Actelion.

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

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with 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 patient (such as Patient Information Leaflet used to obtain informed consent) to an IRB/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 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 patients that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

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

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

The patient and/or legal representative must sign and personally date and time (if appropriate) the ICF before any study-related procedures begin (i.e., any procedures required by the protocol). The ICF must also be signed and personally dated and timed (if appropriate) by the authorized site staff listed on the Delegation of Authority form.

A copy of the signed and dated ICF is given to the patient and/or legal representative; the original is filed in the site documentation.

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

In the case that the site would like to recruit a patient who would be considered as vulnerable (e.g., patient cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure patient 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 such patients are recruited.

13.4 Compensation to patients and investigators

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

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

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any deviation/change from the protocol, except when the change involves only logistical or administrative aspects (e.g., change in telephone number), or in case it would be necessary to eliminate an immediate hazard to the patient.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. IRB/IEC and regulatory authorities must be informed, according to their requirements, but no later than 15 calendar days after the event.

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: investigator's file and patient clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (e.g., 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 investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

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

If the site is using an electronic/computerized system to store patient medical records but it could not be confirmed that the system is validated or if the 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 patient's data. The printouts will be considered as the official clinical study records.

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 patients but at least for some of them (e.g., first patient; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some patients) as per Actelion's instructions. If it were not possible for the 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. The printouts must be filed either with the patient medical records or with the patient's CRF.

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 principal investigator must ensure that all site personnel involved in the study will be 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 patients. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the principal investigator and filed in the Investigative Site File (ISF).

During the study, the monitor will contact and visit the investigational site regularly, and on request must be permitted to have access to trial 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 CRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, and 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 CRFs will be performed according to the study-specific monitoring plan. The frequency of the monitoring visits will be based on patient recruitment rate and critical data collection times.

The principal investigator must ensure that the CRF is completed after a patient's visit to the site, and that all requested patient files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the 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 patient is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

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

13.9 Investigator site file

Each site will be provided with an ISF prior to the 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 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 must 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 principal investigator must inform Actelion immediately.

If the principal investigator 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., patient records) and facilities.

13.11 Inspections

Health Authorities and/or IRB/IEC may also wish to conduct an inspection of Actelion's clinical study during the study or after its completion.

Should an inspection be requested by a Health 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. patient 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.

The coordinating investigator and the Steering Committee 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 its clinical studies on Actelion's Clinical Trial Register (SMADAR), and on external/national registries, as required by 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

[Abman 2009] Abman SH. Role of endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. Annu Rev Med. 2009;60:13-23.

[Addetia 2014] Addetia K, Bhave MN, Tabit CE, Gomberg-Maitland M, Freed BH, Dill KE. Sample size and cost analysis for pulmonary arterial hypertension drug trials using various imaging modalities to assess right ventricular size and function end points. Circ Cardiovasc Imaging. 2014;7:115-124.

[Archer 2013] Archer SL, Fang YH, Ryan JJ, Piao L. Metabolism and bioenergetics in the right ventricle and pulmonary vasculature in pulmonary hypertension. Pulm Circ. 2013 Jan;3(1):144-52.

[ATS Statement 2002] Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002;166:111-7.

[Benigni 1995] Benigni A. Defining the role of endothelins in renal pathophysiology on the basis of selective and unselective endothelin receptor antagonist studies. Curr Opin Nephrol Hypertens 1995;4:349-53.

[Benza 2010] Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS. Predicting survival in pulmonary arterial hypertension insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation. 2010;122:164-172.

[Blalock 2010] Blalock SE, Matulevicius S, Mitchell LC, Reimold D, Warner J, Peshock R. Long-term outcomes with ambrisentan monotherapy in pulmonary arterial hypertension. J Cardiac Fail 2010;16:121-127.

[Bokhari 2011] Bokhari S, Raina A, Rosenweig EB, Schulze PC, Bokhari J, Einstein AJ. PET imaging may provide a novel biomarker and understanding of right ventricular dysfunction in patients with idiopathic pulmonary arterial hypertension. Circ Cardiovasc Imaging. 2011 Nov;4(6):641-7.

[Bradlow 2010] Bradlow WM, Hughes ML, Keenan NG, Bucciarelli-Ducci C, Assomull R, Gibbs JS. Measuring the heart in pulmonary arterial hypertension (PAH): implications for trial study size. J Magn Reson Imaging. 2010 Jan;31(1):117-24.

[Brewis 2016] Brewis MJ, Bellofiore A, Vanderpool RR, Chesler NC, Johnson MK, Naeije R. Imaging right ventricular function to predict outcome in pulmonary arterial hypertension. Int J Cardiol. 2016 Sep 1; 218:206-11

[Brimioulle 2003] Brimioulle S, Wauthy P, Ewalenko P, Rondelet B, Vermeulen F, Kerbaul F. Single-beat estimation of right ventricular end-systolic pressure-volume relationship. Am J Physiol Heart Circ Physiol. 2003 May;284(5): H1625-30.

[Chua 1992] Chua B, Krebs CT, Chua CC, et al. Endothelin stimulates protein synthesis in smooth muscle cells. Am J Physiol 1992;262:E412-6.

[Clarke 1989] Clarke J, Benjamin N, Larkin W, et al. Endothelin is a potent long lasting vasoconstrictor in men. Am J Physiol 1989;257:H2033-5.

[Davie 2002] Davie N, Haleen SJ, Upton PD, et al. ETA and ETB receptors modulate the proliferation of human pulmonary artery smooth muscle cells. Am J Respir Crit Care Med 2002;165:398-405.

[de Nucci 1988] de Nucci G, Thomas R, D Orleans-Juste P, et al. Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin-derived relaxing factor. Proc Natl Acad Sci USA 1988;85:9797-800.

[Fisher 2006] Fisher MR, Mathai SC, Champion HC, Girgis RE, Housten-Harris T, Hummers L. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 2006 Sep;54(9):3043-50.

[Foëx 1994] Foëx P, Leone BJ. Pressure-volume loops: a dynamic approach to the assessment of ventricular function. J Cardiothorac Vasc Anesth. 1994 Feb;8(1): 84-96.

[Franco 2012] Franco V. Right Ventricular Remodeling in Pulmonary Hypertension. Heart Failure Clin 8 (2012):403-412.

[Galiè 2003] Galiè N, Hinderliter AL, Torbicki A, Fourme T, Simonneau G, Pulido T. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension. J Am Coll Cardiol. 2003 Apr 16;41(8):1380-6.

[Galiè 2004] Galiè N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. Cardiovasc Res 2004;61:227-37.

[Galiè 2013] Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. J Am Coll Cardiol 2013;62:D60-72.

[Galiè 2014] Galie N, Albert Barbera J, Frost A, Ardeschir Ghofrani H, Hoeper M, Mclaughlin V et al. AMBITION: A randomised, multicenter study of first-line ambrisentan and tadalafil combination therapy in subjects with pulmonary arterial hypertension (PAH). Eur Respir J. 2014;Suppl 58:44.

[Giaid 1993]. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med. 1993;328: 1732–9.

[Grothues 2003] Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J. 2004 Feb;147(2):218-23.

[Hassoun 2009] Hassoun PM. Therapies for scleroderma-related pulmonary arterial hypertension. Expert Rev Respir Med. 2009;3(2):187-196.

[Hassoun 2015] Hassoun PM, Zamanian, RT, Damico R, et al. Ambrisentan and tadalafil upfront combination therapy in scleroderma-associated PAH. AJRCCM. 2015;192(9):1102-1110.

[Hinderliter 1997] Hinderliter AL, Willis PW, Barst RJ, Rich S, Rubin LJ, Badesch DB, Groves BM. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Primary Pulmonary Hypertension Study Group. Circulation. 1997 Mar 18;95(6):1479-86.

[Hirata 1993] Hirata Y, Emori T, Eguchi S. Endothelin receptor subtype B mediates synthesis of nitric oxide by cultured bovine endothelial cells. J Clin Invest 1993;91:1367-73.

[Hoeper 2006] Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol. 2006 Dec 19;48(12):2546-52.

[Hoeper 2013] Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiol 2013;62:D42-50.

[Humbert 2004] Humbert M, Morell NW, Archer SL, et al. Cellular and Molecular Pathobiology of pulmonary Arterial Hypertension. J Am Coll Cardiol 2004;43: 13S-24S.

[Kasimir 2004] Kasimir MT, Seebacher G, Jaksch P, Winkler G, Schmid K, Marta GM. Reverse cardiac remodelling in patients with primary pulmonary hypertension after isolated lung transplantation. Eur J Cardiothorac Surg. 2004 Oct;26(4):776-81.

[Kuehne 2004] Kuehne T, Yilmaz S, Steendijk P, Moore P, Groenink M, Saaed M. Magnetic resonance imaging analysis of right ventricular pressure-volume loops: in vivo validation and clinical application in patients with pulmonary hypertension. Circulation. 2004 Oct 5;110(14):2010-6.

[Kylhammar 2014] Kylhammar D, Persson L, Hesselstrand R, Rådegran G. Prognosis and response to first-line single- and combination therapy in pulmonary arterial hypertension. Scand Cardiovasc J. 2014 Jun 10:1-23.

[Macitentan IB] Investigator's Brochure. Macitentan ACT-064992. Endothelin receptor antagonist, Version 11. Actelion Pharmaceuticals Ltd, November 2013.

[Massaki 1998] Massaki T. The discovery of endothelins. Cardiovasc Res 1998;39: 530-3.

[O'Callaghan 2011] O'Callaghan DS, Savale L, Montani D, et al. Treatment of pulmonary arterial hypertension with targeted therapies. Nat Rev Cardiol. 2011;8(9):526-38.

[Oudiz 2013] Oudiz RJ. Death in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2013 Aug 1;188(3):269-70.

[Overbeek 2008] Overbeek MJ, Lankhaar JW, Westerhof N, Voskuyl AE, Boonstra A, Bronzwaer JGF. Right ventricular contractility in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. Eur Respir J 2008;31:1161-1166.

[Peacock 2014] Peacock A, Crawley S, McLure L, Blyth K, Vizza CD, Poscia R. Changes in right ventricular function measured by cardiac magnetic resonance imaging in patients receiving pulmonary arterial hypertension-targeted therapy The EURO-MR study. Circ Cardiovasc. Imaging. 2014;7:107-114.

[Pulido 2013] Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani A. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. N Engl J Med 2013;369:809-18.

[Raghu 2013] Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC Trial. Eur Respir J. 2013 Dec;42(6):1622-32.

[Raymond 2002] Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002 Apr 3;39(7):1214-9.

[Rich 1992] Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327(2):76-81.

[Rich 2012] Rich S. Right Ventricular Adaptation and Maladaptation in Chronic Pulmonary Arterial Hypertension. Cardiol Clin. 2012 May;30(2):257-69.

[Roeleveld 2004] Roeleveld RJ, Vonk-Noordegraaf A, Marcus JT, Bronzwaer JG, Marques KM, Postmus PE. Effects of epoprostenol on right ventricular hypertrophy and dilatation in pulmonary hypertension. Chest. 2004 Feb;125(2):572-9.

[Simonneau 2013] Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A. Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol 2013;62:D34-41.

[Sitbon 2005] Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005; 111:3105-11.

[Stewart 1991] Stewart DJ, Levy RD, Cernacek P, et al. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991;114:464-9.

[Sugawara 1996] Sugawara F, Ninomiya H, Okamoto Y, et al. Endothelin-1-inducedmitogenic responses of Chinese hamster ovary expressing human endothelin A: the role of a wortmannin-sensitive signalling pathway. Molec Pharmacol 1996;49:447-57.

[Sunagawa 1980] Sunagawa K, Yamada A, Senda Y, Kikuchi Y, Nakamura M, Shibahara T. Estimation of the hydromotive source pressure from ejecting beats of the left ventricle. IEEE Trans Biomed Eng. 1980 Jun;27(6):299-305.

[Swift 2014] Swift AJ, Rajaram S, Campbell MJ, Hurdman J, Thomas S, Capener D. Prognostic value of cardiovascular magnetic resonance imaging measurements corrected for age and sex in idiopathic pulmonary arterial hypertension. Circ Cardiovasc Imaging. 2014 Jan;7(1):100-6.

[Takeuchi 1991] Takeuchi M, Igarashi Y, Tomimoto S, Odake M, Hayashi T, Tsukamoto T. Single-beat estimation of the slope of the end-systolic pressure-volume relation in the human left ventricle. Circulation. 1991 Jan;83(1):202-12.

[Tedford 2013] Tedford RJ, Mudd JO, Girgis RE, Mathai SC, Zaiman AL, Housten-Harris T. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. Circ Heart Fail. 2013 Sep 1;6(5):953-63.

[Trip 2013] Trip P, Kind T, van de Veerdonk MC, Marcus JT, de Man FS, Westerhof N. Accurate assessment of load-independent right ventricular systolic function in patients with pulmonary hypertension. J Heart Lung Transplant. 2013 Jan;32(1): 50-5.

[Trip 2015] Trip P, Rain S, Handoko ML, van der Bruggen C, Bogaard HJ, Marcus JT, Boonstra A. Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension. Eur Respir J. 2015 Jun; 45(6):1603-12

[Van de Veerdonk 2011] van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol. 2011 Dec 6;58(24):2511-9.

[Van Wolferen 2006] van Wolferen SA, Boonstra A, Marcus JT, Marques KM, Bronzwaer JG, Postmus PE. Right ventricular reverse remodelling after sildenafil in pulmonary arterial hypertension. Heart. 2006 Dec;92(12):1860-1.

[Van Wolferen 2011] van Wolferen SA, van de Veerdonk MC, Mauritz GJ, Jacobs W, Marcus JT, Marques KM. Clinically significant change in stroke volume in pulmonary hypertension. Chest. 2011 May;139(5):1003-9.

[Van Wolferen 2007] van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J. 2007 May;28(10):1250-7.

[Vonk-Noordegraaf 2011] Vonk-Noordegraaf A, Galiè N. The role of the right ventricle in pulmonary arterial hypertension. Eur Respir Rev. 2011;20(122):243-253.

[Wilkins 2005] Wilkins MR, Paul GA, Strange JW, Tunariu N, Gin-Sing W, Banya WA. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. Am J Respir Crit Care Med. 2005 Jun 1;171(11):1292-7.

[Yamada 2012] Yamada Y, Okuda S, Kataoka M, Tanimoto A, Tamura Y, Abe T. Prognostic value of cardiac magnetic resonance imaging for idiopathic pulmonary arterial hypertension before initiating intravenous prostacyclin therapy. Circ J. 2012;76(7):1737-43.

Appendix 1 Actelion guidelines for RHC

RIGHT HEART CATHETERIZATION

These guidelines should be followed where possible. If historical RHC data have been used at baseline according to inclusion criterion 5 and do not fully comply with these guidelines, any post-baseline RHC must be performed in the same way as the baseline RHC to ensure data consistency.

1 Material and methods

- Patients will undergo right heart catheterization (RHC) at the study site or other institution in case no suitable laboratory is available at the study site in an appropriate care setting (e.g., cardiac catheterization laboratory, medical procedures unit, intensive care unit). Left heart catheterization, if needed, must be carried out in the cardiac catheterization laboratory.
- Hemodynamic evaluations will be carried out with the patient in the supine position. Patients will breathe room air. If the patient requires supplemental oxygen during catheterization, oxygen must be given during both baseline and the follow-up assessments (if applicable). Electrocardiogram for the assessment of the heart rate (HR) will be monitored continuously. Systolic and diastolic systemic arterial pressures (sSAP, dSAP) will be measured by the cuff method at the brachial artery level.
- RHC will be performed according to laboratory's standard procedures through the internal jugular, subclavian, or femoral vein by a balloon catheter placed into either the right or left pulmonary artery. A triple-lumen, balloon-tipped thermodilution catheter will be used for measurement of selected intracardiac pressures (at end-expiration) and cardiac output (CO). A four-lumen, balloon-tipped thermodilution catheter can be used, if obtaining accurate pulmonary capillary wedge pressure (PCWP) or pulmonary arterial pressure (PAP) is problematic.
- CO will be measured by thermodilution.
- For those patients on background medication that includes anticoagulants (e.g., warfarin), the usual safety measures, as routinely used by the study site for cessation of these drugs prior to and after the procedure, must be taken.

2 Assessments

2.1 *Hemodynamic parameters measured during RHC:*

- HR
- CO

- Pulmonary artery pressure (systolic, diastolic, electronic mean: sPAP, dPAP, mPAP)
- Mean right atrial pressure (mRAP)
- PCWP or left atrial end diastolic pressure (LVEDP). See Section 2.3.
- Noninvasive sSAP and dSAP)

2.2 *Measurement and selection of hemodynamic parameters:*

- Hemodynamic pressures (mPAP, mRAP, and PCWP, or LVEDP) will be measured in duplicate (10 minutes apart), or until 2 consecutive values do not differ > 10%: the last value will be recorded in the RHC page of the Case Report Form (CRF).
- For the measure of PCWP, the same method must be used consistently throughout the study.
- HR and systemic arterial pressure: will be measured in duplicate (10 minutes apart), or until 2 consecutive values do not differ > 10%: the last value will be recorded in the RHC page of the CRF.
- CO will be measured in triplicate, or until 3 consecutive values do not differ > 10%: the mean value will be recorded in the RHC page of the CRF.
- All measured hemodynamic values, including those not reported in the RHC page of the CRF, and the time when the measurements were taken must be included in the catheterization report or recorded in a source document.

2.3 *Calculated hemodynamic parameters:*

- Pulmonary vascular resistance (dyn.sec.cm^{-5}): $PVR = \left(\frac{mPAP-PCWP}{CO}\right) * 80$
- Total pulmonary vascular resistance (dyn.sec.cm^{-5}): $TPR = \frac{mPAP}{CO}$*80
- Cardiac index (l.min^{-1}.m^{-2}): $CI = \frac{CO}{BSA}$
- Body surface area (m^2): $BSA = 0.007184 * (weight^{0.425}) * (height^{0.725})$

with weight expressed in kg and height in cm.

2.4 *Data transmission for central assessment:*

Right ventricle and pulmonary artery pressure signals over at least 10 heartbeats, simultaneous with ECG sampling, is requested. Sample frequency must be at least 200Hz. Pressure calibration must be provided. Pressure curves will be uploaded in a specially designed web site and will be centrally assessed.

Appendix 2 Actelion guidelines for 6MWT

The American Thoracic Society (ATS) published an official statement on the 6-minute walk test (6MWT) in 2002 [ATS Statement 2002]. Only a brief summary of these guidelines is included here.

- The 6MWT must be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The use of treadmill is forbidden.
- The walking distance used for the test must be 30 meters (100 feet) in length. This distance should be marked every 3 meters (10 feet). The turnaround point should be marked with a cone. A starting line, which marks the beginning and the end of each 60-meter lap, should be marked on the floor using brightly colored tape. Any deviation from this must be approved in written form by Actelion before implementation.
- The study staff member administering the 6MWT will stand near the starting line during the test and must not walk with the patient! Intermittent rest periods are allowed if the patient can no longer continue. If the patient needs to rest, he/she may pause, lean against the wall or sit and should continue walking whenever he/she feels able. The timer must continue to run. The test can be stopped at any moment in case the patient complains of having chest pain, intolerable dyspnea, leg cramps, or has a pale or ashen appearance.
- The 6MWT is a non-encouraged test. No instructions or encouragement will be given during the test. Eye contact and body language signaling the patient to speed up should be avoided during the test.
- For an individual patient, repeat testing must always be conducted, if possible, by the same tester, at the same location, and preferably at about the same time of the day to minimize variability.

Required equipment:

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

Patient preparation

- The patient should wear comfortable clothing and appropriate walking shoes.
- The meals preceding the test should be light, and the patient should not have exercised vigorously within 2 hours of beginning the test.
- The patient should sit at rest for at least 10 minutes before the test starts.
- Patients must receive their usual medication on the day of the test. If the patient is used to taking bronchodilators before a walk, he/she should take them 5–30 minutes before the test.
- For patients receiving continuous 24-hour oxygen therapy, it is recommended that the flow rate remains constant for the duration of the study. However, from one hour prior to and until the completion of the 6MWT, the flow rate must remain constant.

Measurement of the 6MWD/6MWT – Instructions to the patient

The person administering the test will use the following exact dialogue with the patient: "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation".

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

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

"Do you have any questions about the test?"

"Please explain what you are going to do."

"Are you ready?"

"Start now, or whenever you are ready."

As soon as the patient starts to walk, the tester will start the timer and write down start time.

The tester will tell the patient the time elapsed by saying:

“You have 4 minutes to go.”

“You have 2 minutes to go.”

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

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

When the timer alarm rings the tester says:

“Stop!”

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

Appendix 3 Borg dyspnea index

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

Appendix 4 WHO Functional Classification of pulmonary hypertension

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

Appendix 5 Study drug storage

The investigator is responsible for safe and proper handling and storage of the study drug at the investigational site, and for ensuring that the study drug is administered only to patients enrolled in the study, in accordance with the protocol.

Study drug must be kept in a locked room, or a locked cupboard in a restricted access room, which can be accessed only by the pharmacist, the investigator, or another duly designated person as specified on the Delegation of Authority form.

The study drug must be stored below 30 °C and must be protected from moisture. Unopened, sealed study medication bottles may be stored in refrigerators (between the temperature range of +2 °C to 30 °C). If the temperature at a patient's home exceeds 30 °C, the patient must be instructed to store the unopened bottles of the study drug in his/her refrigerator. Frozen storage (below +2 °C) is not permitted. Unsealed bottles **must not** be stored in the refrigerator.

At the site, a temperature log must be maintained, and temperature control should occur at least on a weekly basis.

Actelion will provide a temperature log if not available on site, however, the use of the log is not mandatory if the site has an acceptable means of recording the temperature. Any temperature-recording system routinely used at the site is acceptable, as long as all required information is included and certification of calibration is provided. If the temperature is captured electronically, a printout must be made available to the monitor during each on-site visit.

In case a deviation from the defined temperature range is identified by the site, the deviation is to be reported to the monitor, preferably in writing and with supportive documentation (e.g., a copy of the temperature log showing data for all excursion days). The monitor must immediately notify Actelion for further advice. The study drug affected by a deviation will not be used (e.g., segregated physically at the investigational site) until confirmation by Actelion that it is safe to be used. In case the temperature deviation is defined as acceptable, a corresponding message is returned to the site via the monitor.

In case the temperature deviation is defined as not acceptable and the quality of the study drug might be affected, the study drug is kept segregated at the investigational site and returned to Actelion following internal drug return processes. New study drug supplies will be provided to the site.

Site temperature deviations correspondence must be kept in the Investigator Site File. The study centers will be supplied with the study drug according to the centers' needs, depending on the rate of patient enrollment.

Appendix 6 Central laboratory

In case of laboratory abnormalities at any visit corresponding to the thresholds below, the central laboratory will alert Actelion and the concerned site. Alert flags will trigger these notifications.

Analyte	**Threshold**
ALT	≥ 3 × ULN
AST	≥ 3 × ULN
Hemoglobin	< 80 g/L, *or* Decrease by > 20g/L from last value before study drug initiation
Beta-human chorionic gonadotropin	> 5 mIU/ml

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

Appendix 7 Eligibility questionnaire

Site Identification
Principal Investigator _____
Patient Identification
Patient number └┴┴┴┴┴┴┴┘ ***Age*** └┴┘
Please complete the questionnaire below to document which tests/procedures have been performed in order to exclude other causes of pulmonary hypertension for the patient indicated above. This questionnaire must be completed prior to treatment initiation for all patients: a) with 30 < BMI < 35 kg/m^2, *and/or* b) with 65 ≤ Age < 75 years

1. Patient characteristics

Body mass index └┴┘.└┘ kg/m^2

Gender ☐Male ☐Female

PAH etiology ☐ Idiopathic PAH

☐ Heritable PAH

☐ Drug- and toxin-induced PAH

☐ PAH associated with connective tissue disease

☐ PAH associated with congenital heart diseases, only simple congenital systemic to pulmonary shunts at least 2 year post surgical repair

Most recent Right Heart Catheterization date: └┴┘ └┴┴┘ └┴┘
dd mmm yy

mPAP:

PVR:

PCWP:

LVEDP:

If RHC curves are available, please provide them.

	Ongoing	**Not ongoing**
Relevant medical history: ----------		

	Yes	**No**
2. Was an echocardiography performed?	☐	☐
a. If yes, date of the most recent echocardiography: ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ dd mmm yy		
b. If yes, did it show		
i. left ventricular systolic dysfunction?	☐	☐
ii. left ventricular diastolic dysfunction?	☐	☐
iii. enlarged left ventricle ?	☐	☐
iv. enlarged left atrium?	☐	☐
v. left-sided valvular heart disease?	☐	☐
If you have answered "Yes" to one or more of the questions above, how did you exclude this/these finding(s) as the main reason for pulmonary hypertension? ----------		

--- --- --- --- --- ---		
	Yes	**No**
2. Was a ventilation/perfusion lung scan performed? ☐ a. If yes, date of the most recent scan: **Ventilation Scan** L_L_ L_L_L_ L_L_ dd mmm yy **Perfusion Scan** L_L_ L_L_L_ L_L_ dd mmm yy b. If yes, did it show significant perfusion defects? ☐ If you have answered "Yes" to the question above, how did you exclude pulmonary thromboembolism as the main reason for pulmonary hypertension? --- --- --- --- ---	☐ ☐	☐ ☐
3. Were lung function tests performed? ☐ a. If yes, date of the most recent lung function tests: **Spirometry** L_L_ L_L_L_ L_L_ dd mmm yy **Body Plethysmography** L_L_ L_L_L_ L_L_ dd mmm yy	☐	☐

b. If yes, did it show i. $FEV_1/FVC < 70\%$? ..... ii. $FEV_1 < 65\%$ of predicted value? ..... iii. Total Lung Capacity < 60% of predicted value? ..... If you have answered "Yes" to one or more of the questions above, how did you exclude moderate to severe obstructive lung disease or moderate to severe restrictive lung disease as the main reason for pulmonary hypertension? --- --- --- --- ---	☐ ☐ ☐	☐ ☐ ☐
	Yes	**No**
1. Were any other relevant tests (e.g., contrast-enhanced computed tomography, spiral computed tomography, high resolution computed tomography, magnetic resonance imaging) performed to exclude other etiology than PAH?	☐	☐
2. If yes, which type of test(s) and when (indicate most recent)? i. ---------- ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ dd mmm yy ii. ---------- ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ dd mmm yy iii. ---------- ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ dd mmm yy Please briefly describe the results of this/these procedures(s) 3. --- --- --- --- --- --- ---		

Investigator name:		
Date (DDMMMYYYY):	Investigator signature:	

Please email form to [redacted]

CRA name, signature and date AFTER SDV performed: