Macitentan / ACT-064992

Pulmonary hypertension post-left ventricular assist device implantation

Protocol AC-055-205

SOPRANO: Macitentan in pulmonary hypertenSiOn Post-left ventRiculAr assist device implaNtatiOn

A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation

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Treatment name / number

Macitentan / ACT-064992

Indication

Pulmonary hypertension post-left ventricular assist device implantation

Protocol number, study acronym, study title

AC-055-205, SOPRANO: A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation

I approve the design of this study.

TITLE	NAME	DATE	SIGNATURE
Clinical Trial Physician	Mona Selej, M.D., M.S., Associate Director, Medical Affairs	10 Mar 2017	PPD
Clinical Trial Statistician	Carol Zhao, M.S. Associate Director, Biostatistics	10 Mar 2017	

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

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AC-055-205, SOPRANO: A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation.

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

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

	Country	Site number	Town	Date	Signature
Principal Investigator					

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LIST OF ABBREVIATIONS AND ACRONYMS

2D	Two-dimensional
3D	Three-dimensional
6MWD	6-minute walk distance
A’	Tricuspid peak diastolic annular velocity a’
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Cardiac index
CL	Confidence limit
CO	Cardiac output
CRA	Clinical research associate
CRO	Contract Research Organization
CV	*Curriculum vitae*
CVs	Coefficients of variation
CYP3A4	Cytochrome P450 isozyme 3A4
DBP	Diastolic blood pressure
DoA	Delegation of Authority
DT	Destination therapy
E’	Tricuspid peak diastolic annular velocity e’
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1

ET_A	Endothelin receptor A
ET_B	Endothelin receptor B
FAS	Full Analysis Set
FC	Functional class
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GDF-15	Growth differentiation factor-15
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
HF	Heart failure
hsCRP	High sensitivity C-reactive protein
hs-cTnT	High sensitivity cardiac troponin T
i.v.	Intravenous
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference On Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL-6	Interleukin-6
iNO	Inhaled nitric oxide
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
IxRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LFT	Liver function test

LVAD	Left ventricular assist device
MedDRA	Medical Dictionary For Regulatory Activities
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
NGAL	Neutrophil gelantinase-associated lipocalin
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PAC	Pulmonary artery catheter
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PDE5	Phosphodiesterase-5
PH	Pulmonary hypertension
PI	Principal investigator
PPS	Per-Protocol Set
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RRT	Renal replacement therapy
RV	Right ventricle
RVAD	Right ventricular assist device
RVF	Right ventricular failure
RVFAC	Right ventricular fractional area change
RVLS	Global RV longitudinal strain
RVSI	Right ventricular sphericity index
s.c.	Subcutaneous
S’	Tricuspid peak annular velocity s’
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SIV	Site initiation visit
SOC	System organ class
SOP	Standard operating procedure

SOPRANO	Macitentan in pulmonary hypertension post-left ventricular assist device implantation
SS	Safety Set
ST2	Member of the interleukin 1 receptor family
SUSAR	Suspected unexpected serious adverse reaction
SVO_2	Mixed venous oxygen saturation
TAH	Total artificial heart
TAPSE	Tricuspid annular plane systolic excursion
TNF-α	Tumor necrosis factor- α
TPR	Total pulmonary resistance
ULN	Upper limit of the normal range
WHO	World Health Organization
WU	Wood unit

SUBSTANTIAL GLOBAL AMENDMENT 2

Amendment rationale

This amendment[1] applies to protocol AC-055-205 Version 2, dated 25 August 2015. The resulting amended global protocol is Version 3, dated 10 March 2017.

The main reason for this amendment is to extend the 45-day post-left ventricular assist device Screening window to 90 days.

Other changes include:

- Addition of a Glossary to clarify protocol terms.
- Sample size re-estimation updates based on recently released study results (e.g., MERIT).
- Re-definition of Baseline right heart catheterization (RHC) with emphasis on the required thermodilution method for Baseline and Week 12 (End-of-Treatment) RHC.
- Removal of any language pertaining to pulmonary artery catheter (PAC) assessments (as PAC serving as the source of Baseline RHC hemodynamics is expected to be rare).
- Addition of the requirement that Randomization must take place within 14 days of Baseline RHC (new inclusion criterion).
- General text edits for greater clarity in study execution and training.
- Description of the core responsibilities of the Clinical Event Committee and Core Hemodynamics Laboratory.
- Primary, secondary and exploratory efficacy analyses to be performed on the Full Analysis Set (FAS), no longer the modified FAS.

Changes to the protocol

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

[1] This amendment is global amendment 2, applicable to all sites in the study. The previous amendment was local amendment 1 (US). However, as this study only has sites in the US, the amendment type has been revised to 'global' to clarify that it is applicable to all sites in the study.

Amended protocol sections

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

1.5.5	Summary of potential risks and risk management
3.1	Study design
3.3	Study committees
4.2	Rationale for the selection of the study population
4.3	Inclusion criteria
4.4	Exclusion criteria
5.1.3	Study treatment administration
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11.5.1	Sample size justification
11.5.2	Sample size sensitivity
13.8	Monitoring

Summary of previous amendments

Amendment	Date	Main reason(s)
1	25 August 2015	The hemodynamic variables decided on by the AC-055-205 study team and approved by Protocol Approval Committee were listed correctly in the protocol synopsis and Section 4.2 of the final protocol. However, the updated hemodynamic variables were not incorporated in Section 4.3 of the final protocol. The amendment was to reflect the accurate inclusion criteria and to have consistency across the sections of the protocol.

PROTOCOL SYNOPSIS AC-055-205

TITLE	A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation.
ACRONYM	**SOPRANO:** Macitentan in pulmonary hypertens**S**i**O**n **P**ost-left vent**R**icul**A**r assist device impla**N**tati**O**n
OBJECTIVES	**Primary objective** To evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) as compared to placebo in subjects with pulmonary hypertension (PH) after left ventricular assist device (LVAD) implantation. **Secondary objectives** • To evaluate the effect of macitentan 10 mg as compared to placebo on cardio-pulmonary hemodynamics and disease severity in subjects with PH after LVAD implantation. • To evaluate the safety and tolerability of macitentan 10 mg in subjects with PH after LVAD implantation. **Exploratory objectives** • To explore the potential effect of macitentan 10 mg as compared to placebo on right ventricular function in subjects with PH after LVAD implantation. • To explore the potential effect of macitentan 10 mg as compared to placebo on selected clinical events in subjects with PH after LVAD implantation. • To explore the potential effect of macitentan 10 mg as compared to placebo on renal function as measured by the glomerular filtration rate (GFR) in subjects with PH after LVAD implantation.
DESIGN	Prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 2 study.

PERIODS	**Screening period:** Up to 90 days from LVAD implantation until Randomization. **Treatment period:** From Randomization up to Week 12 or earlier in case of premature discontinuation of study treatment. Subjects who prematurely discontinue study treatment must have an End-of-Treatment (EOT) visit within 7 days of study treatment discontinuation. **Study treatment** is defined as the dosing (intake) by the subject of double-blind study drug (macitentan or placebo). **Post-treatment safety follow-up period:** Subjects who complete the treatment period as planned, i.e., full 12-week study period, and those who prematurely discontinue study treatment, will enter a 30-day safety follow-up period which ends with the End-of-Study (EOS) visit at least 30 days after the permanent discontinuation of study treatment.
PLANNED DURATION	Approximately 36 months from first subject, first visit to last subject, last visit.
SITE(S) / COUNTRY(IES)	Approximately 50 clinical sites in the United States.
SUBJECTS / GROUPS	78 subjects in 2 groups, randomized in a 1:1 ratio by an Interactive Voice/Web Randomization System to macitentan 10 mg or placebo.
INCLUSION CRITERIA	1 Written Informed Consent prior to initiation of any study-mandated procedure. 2 Males or females ≥ 18 years of age. 3 Surgical implantation of LVAD within 90 days prior to Randomization. 4 Hemodynamic evidence of PH on Baseline right heart catheterization (RHC) by the thermodilution method. Baseline RHC is defined as the last hemodynamic measurements after LVAD implantation and prior to the first dose of study treatment. PH is defined as: a) Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg *and* b) Pulmonary artery wedge pressure (PAWP) ≤ 18 mmHg *and* c) PVR > 3 Wood units.

INCLUSION CRITERIA (cont'd)	5 Stabilization of the patient for 48 h prior to the Baseline RHC, defined as: a) No LVAD pump speed/flow rate changes *and* b) Stable dose of oral diuretics *and* c) No intravenous (i.v.) inotropes or vasopressors *and* d) Patient able to ambulate. 6 A woman of childbearing potential is eligible *only* if she has: a) A negative serum pregnancy test result during the Screening period (Visit 1) and Randomization (Visit 2) *and* b) Agreement to undertake monthly serum pregnancy tests during the study and up to 30 days after study treatment discontinuation *and* c) Agreement to use one of the methods of contraception / follow the contraception scheme described in Section 4.5 from Screening and up to *at least 30 days after* study treatment discontinuation. 7 Patient must be randomized within 14 days of Baseline RHC.
EXCLUSION CRITERIA	1 Documented severe obstructive lung disease defined as: forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC) < 0.7 associated with FEV_1 < 50% of predicted value after bronchodilator administration. 2 Documented moderate to severe restrictive lung disease defined as: total lung capacity < 60% of predicted value. 3 Documented pulmonary veno-occlusive disease. 4 Patients undergoing dialysis. 5 Hemoglobin < 8.5 g/dL at Randomization. 6 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) at Randomization. 7 Severe hepatic impairment, e.g., Child-Pugh Class C liver disease. 8 Body weight < 40 kg at Randomization. 9 Doppler mean blood pressure < 65 mmHg at Randomization. 10 GFR < 30 mL/min at Randomization. 11 Pregnant, planning to become pregnant during the study period, or breastfeeding.

EXCLUSION CRITERIA (cont'd)	12 Treatment with endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE5) inhibitors, i.v., subcutaneous (s.c.), or oral prostanoids, or guanylate cyclase stimulators within 7 days prior to Baseline RHC or study treatment initiation. 13 Treatment with inhaled prostanoids (e.g., iloprost, epoprostenol) or nitric oxide within 24 h prior to Baseline RHC or study treatment initiation. 14 Treatment with strong inducers of cytochrome P450 isozyme 3A4 (CYP3A4) within 28 days prior to study treatment initiation (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort). 15 Treatment with strong inhibitors of CYP3A4 within 28 days prior to study treatment initiation (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, saquinavir, boceprevir, telaprevir, iopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, and idinavir). 16 Treatment with another investigational drug (planned, or taken) within 28 days prior to study treatment initiation. 17 Known hypersensitivity to ERAs, or to any of the study treatment excipients. 18 Any condition that prevents compliance with the protocol or adherence to therapy. 19 Known concomitant life-threatening disease with a life expectancy < 12 months.
STUDY TREATMENTS	**Investigational treatment** Macitentan oral tablet, 10 mg once daily. **Comparator and/or placebo** Matching placebo, once daily.
CONCOMITANT THERAPY	**Allowed concomitant medication** Oral and i.v. diuretics are allowed and may be adjusted during the treatment period. (Treatment with oral diuretics is allowed if ongoing at a stable dose for at least 48 h prior to the Baseline RHC.)

CONCOMITANT THERAPY (cont'd)	**Prohibited concomitant medications** • Pulmonary arterial hypertension-specific therapy (ERAs, i.v., s.c., inhaled or oral prostanoids, PDE5 inhibitors, guanylate cyclase stimulators). • Inhaled nitric oxide. • Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir,saquinavir, boceprevir, telaprevir, iopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, and idinavir) and strong inducers of CYP3A4 (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort). • Any investigational drug. Initiation of one of these prohibited medications will lead to premature discontinuation of study treatment.
LVAD Flow Rate	**Allowed LVAD Flow Rate** The LVAD pump speed/flow rate may be adjusted during the treatment period and during the Baseline RHC. (LVAD pump speed/flow rate must be stable for at least 48 h prior to the Baseline RHC).
ENDPOINTS	**Definitions** Baseline is defined as the last value obtained prior to first dose of study treatment. **Primary efficacy endpoint** PVR ratio of Week 12 to Baseline. PVR is obtained by the thermodilution method. **Secondary efficacy endpoints** Change from Baseline to Week 12 in mean right atrial pressure, mPAP, PAWP, cardiac index (CI), total pulmonary resistance, and mixed venous oxygen saturation, all measured at rest. Change in NT-proBNP from Baseline to Week 12. Change in WHO functional class from Baseline to Week 12.

ENDPOINTS (cont'd)	**Exploratory efficacy endpoints** Change in echocardiographic variables from Baseline to Week 12. These variables include: • 2D global RV longitudinal strain • RV sphericity index • RV end systolic area • RV end diastolic area • Tricuspid annular plane systolic excursion • Tricuspid peak annular velocity s' • RV fractional area change • Tricuspid peak diastolic annular velocities e', a' Time to first encounter of clinical events, from enrollment to Week 12. These clinical events include: • Hospital admission for heart failure (HF) • Re-initiation of i.v. diuretics ≥ 48 h duration • Re-initiation of i.v. inotropes ≥ 48 h duration • Initiation of PDE5 inhibitors • Need for right ventricular assist device / total artificial heart • Need for renal replacement therapy • Death. Days in the hospital after hospitalization for HF. Change in GFR from Baseline to Week 12. **Safety endpoints** 1 Treatment-emergent adverse events (AEs) up to 30 days after study treatment discontinuation. 2 AEs leading to premature discontinuation of study treatment. 3 Death up to 30 days after study treatment discontinuation. 4 Treatment-emergent serious adverse events (SAEs) up to 30 days after study treatment discontinuation. 5 Change from Baseline to EOT in vital signs. 6 Occurrence of liver function test (ALT and/or AST) abnormality (≥ 3 × ULN; ≥ 3 and < 5 × ULN; ≥ 5 and < 8 × ULN; ≥ 8 × ULN) up to EOT. 7 Occurrence of ALT and/or AST abnormality ≥ 3 × ULN associated with bilirubin ≥ 2 × ULN up to EOT.

	8 Proportion of patients with treatment-emergent hemoglobin abnormality (< 10.0 g/dL, and < 8.0 g/dL) as compared to Baseline up to EOT. 9 Treatment-emergent marked laboratory abnormalities up to EOT.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	**Analysis sets** The Screened Analysis Set includes all patients who were screened and received a Screening number. The Safety Set (SS) includes all patients who received at least one dose of study drug in the double-blind treatment period. The Full Analysis Set (FAS) includes all patients randomized. The modified FAS includes all patients in the FAS that have received at least one dose of study drug in the treatment period and have a Baseline, and at least one post-Baseline, PVR measurement. The Per-Protocol Set (PPS) comprises all patients included in the modified FAS without major protocol deviations. **Primary efficacy variable** The primary efficacy variable is the PVR ratio of Week 12 to Baseline. **Statistical hypotheses** The null hypothesis is that the mean PVR ratio is the same in the macitentan and placebo groups. The alternative hypothesis is that the mean PVR ratio is lower in the macitentan group as compared to the placebo group. **Type-I and -II errors and power** The type I error (α) is set to 0.025 (one-sided), the type II error is set to 0.20 and the power to 80%. **Sample size calculation** There are no randomized trial data in this patient population. However, an integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), the hemodynamic sub-study of SERAPHIN (AC-055-302), and the recently completed MERIT study (AC-055E201) of macitentan

STATISTICAL METHODOLOGY (cont'd)	in patients with inoperable chronic thromboembolic pulmonary hypertension, suggest that the treatment group difference on PVR is around −0.28 on log scale (ranged from −0.45 to −0.17 with 95% confidence interval: −0.35, −0.21) and that the within group standard deviation is around 0.40 (90% confidence interval: 0.38, 0.42) on log scale. Under assumptions of the treatment group difference −0.28 and the within group standard deviation 0.41 on log scale, 70 evaluable patients will be needed for 80% power (35 patients per group). Accounting for 10% non-evaluable patients, 78 patients will need to be randomized. **Primary analysis** The primary analysis will be performed on the FAS. The Week 12 versus Baseline ratio in PVR will be log-transformed (base e) and analyzed using an analysis of covariance with a factor for treatment group and a covariate for Baseline log PVR. The treatment group difference in mean change from Baseline (on log scale) and its 95% CI will be estimated based on the model. The geometric mean ratio (GMR; macitentan vs. placebo) and its 95% CI will be obtained by exponentiation. The null hypothesis will be rejected if the entire 95% CI is below one. The treatment effect will be expressed as (GMR−1) × 100%, where a negative value indicates a reduction of PVR in the macitentan group as compared to the placebo group. If PVR cannot be calculated due to missing PAWP but mPAP and cardiac output are available for the same visit, PAWP will be imputed. In patients with a post-Baseline PVR measurement obtained before Week 12, the last post-Baseline PVR measurement will be carried forward. If a patient has no post-Baseline PVR measurement, the ratio of Week 12 to Baseline PVR will be imputed using the treatment group median based on the FAS. Patients who do not have Baseline PVR will be not evaluable and excluded from the analysis.

	Secondary and exploratory analyses Secondary and exploratory efficacy variables will be analyzed on the FAS at $\alpha = 0.025$ (one-sided) using 95% confidence limits. No correction for multiple testing will be applied for these analyses. **Safety endpoints** Safety data including AEs and SAEs will be summarized using the SS.
STUDY COMMITTEES	A Steering Committee is involved in the study design and will be consulted prior to and during the study for relevant medical issues and study publications. An Independent Data Monitoring Committee (IDMC), with members representing the specialties of cardiology and biostatistics, has overall responsibility for safeguarding the interests of subjects by monitoring data from the study and may recommend modification, discontinuation, or completion of the study. The composition and operation of the IDMC is described in the IDMC charter. A Clinical Event Committee (CEC) is an independent committee appointed by Actelion to review blinded data on hospital admission events for HF and death due to any cause. This standardized assessment of HF admission events is expected to limit variability and potential for bias associated with site-based event(s). The composition and operation of the CEC is described in the CEC charter. A Core Hemodynamics Laboratory (CHL) has been appointed to review RHC tracings to allow for a standardized assessment of data quality. The RHC tracings data will be recorded by the CHL in a CHL Case Report Form, entered into the study database, and analyzed for variability. Services of the CHL are governed by a CHL charter.

Table 1 Visit and assessment schedule

PERIODS	Name	SCREENING	DOUBLE-BLIND TREATMENT					FOLLOW-UP
	Duration	Up to 90 days	12 Weeks					30 days
VISITS	Number	1	2	3	4	5	U1, U2, etc.	6
	Name	Screening[1a]	Randomization[1b]	Week 4	Week 8	Week 12 or EOT[2]	Unscheduled Visit[3]	EOS[4]
	Time	Day −90 to Day −1	Day 1	Day 28 (± 7 days)	Day 56 (± 7 days)	Day 84 (± 7 days)	Any day between Days 1 and 84	30 days (+ 7 days) after last dose
Informed Consent		X						
Eligibility		X						
Randomization			X					
Demographics & baseline characteristics		X						
Medical history		X						
Medications		X	X	X	X	X	X	X
Physical examination[5]		X				X	X	
Vital signs, body weight, height and BMI[6]		X	X			X	X	
Screening laboratory tests		X[7a]	X[7a]					
Central laboratory tests			X[7b]	X	X	X	X	X
Contraception check & Pregnancy test[8]		X	X	X	X	X	X	X
RHC by the thermodilution method		X[9a]				X[9b]	X[9c]	
Echocardiography			X[10]			X	X[11]	
NT-proBNP			X			X	X	
WHO functional class			X			X	X	
Study treatment dispensing/return			X	X	X	X[12]	X	
AEs and SAEs[13]		X	X	X	X	X	X	X

[1a] Written Informed Consent must be obtained prior to initiation of any study-mandated procedures. Screening and Randomization visits may be conducted on the same day, provided eligibility is confirmed and all study-mandated procedures are completed prior to Randomization.
[1b] Randomization must be within 14 days of Baseline RHC. Study treatment starts immediately after Randomization.
[2] EOT must occur on the day of the last dose of study treatment or within 7 days of study treatment discontinuation if prior to Week12 (Day 84).
[3] Unscheduled Visits can be performed at any time during the study, as necessary, at the investigator's discretion. Study specific procedure/assessments that are marked (X) may be performed during an Unscheduled Visit, and corresponding data will be collected in the eCRF.
[4] Subjects who complete the study as planned, i.e., full 12-week study period and those who prematurely discontinue study treatment will enter a 30-day safety follow-up period, which ends with the EOS visit at least 30 days after the permanent discontinuation of study treatment.
[5] Clinically relevant findings at the time of signing of Informed Consent must be recorded on the Medical History eCRF page. Findings made after signing of informed consent, and which meet the definition of an AE [Section 10.1.1], must be recorded on the AE page of the eCRF.
[6] Height is only measured at Screening (in cm).
[7a] At the time of Screening, local laboratory results may be used for determination of subject status (e.g., guiding RHC decision-making). At the time of Randomization, local laboratory results will be used to determine subject eligibility.
[7b] Central lab results must be collected and submitted once eligibility is confirmed and prior to Randomization. Laboratory testing includes hematology and blood chemistry. Additionally, NT proBNP, biomarkers and calculated GFR will be performed on Visits 2 and 5.
[8] For women of childbearing potential only. Randomization (Visit 2) pregnancy test result must be negative prior to Randomization.
[9a] The last hemodynamic measurements after LVAD implantation and prior to the first dose of study treatment. Randomization must be within 14 days of Baseline RHC.
[9b] Repeated at Week 12 or within 7 days of permanent discontinuation of study treatment if prior to Week 12. All RHC hemodynamics must be obtained by the thermodilution method.
[9c] RHC may be performed at an Unscheduled Visit, and must be recorded in the eCRF. If the Unscheduled RHC is the last RHC, the data should be entered as Week 12 or EOT RHC (see 9[b]). If the Unscheduled RHC is before the last (Week 12 or EOT) RHC, the data should be entered as Unscheduled Visit.
[10] Baseline ECHO must occur on the day of Randomization.
[11] ECHO may be performed at an Unscheduled Visit, and must be recorded in the eCRF.
[12] If study treatment discontinuation occurs prior to Week 12 (Day 84), record drug return as per standard procedure (e.g., on the eCRF Study Drug Dispensing and Accountability form).
[13] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation **must** be reported in the eCRF.

AE = adverse event; BMI = body mass index; eCRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; GFR = glomerular filtration rate; LVAD = left ventricular assist device; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SAE = serious adverse event; WHO = World Health Organization.

PROTOCOL

1 BACKGROUND

1.1 Indication

End-stage heart failure (HF) is a debilitating condition for which heart transplant offers the best treatment option, but the need for donor hearts greatly exceeds supply. This shortage of donor hearts underscores the need for alternative treatment options. Since the first approval by the Food and Drug Administration (FDA) of a left ventricular assist device (LVAD) as bridge to transplant in 1994 and as destination therapy (DT) in 2002, LVADs have become an increasingly frequent treatment option for patients with end-stage HF [Rommel 2014]. In patients with advanced HF, the use of continuous flow LVADs results in clinically meaningful survival benefits and improved quality of life [Rose 2002, Slaughter 2009].

While LVADs improve left-sided hemodynamic variables, right ventricular failure (RVF) occurring after the implantation of LVADs is a major cause of morbidity and mortality [Patlolla 2013, Grant 2012]. Pre-operative right ventricular dysfunction often does not improve after left ventricular mechanical unloading and may even worsen. Persistently elevated pulmonary vascular resistance (PVR) is associated with RVF after LVAD implantation [Rommel 2014]. Patlolla et al suggest that LVADs cause geometrical and functional changes in the right ventricle (RV) [Patlolla 2013]. The dynamic change in ventricular interdependence, ventriculo-arterial coupling, afterload and preload following LVAD insertion may determine RV compensation following LVAD. Patients with baseline dilated RV, decreased RV contractility, or severely increased stiffness may be particularly susceptible to ventriculo-arterial uncoupling and RVF after LVAD insertion.

The indication of this study is pulmonary hypertension (PH) appearing, maintaining, or worsening after LVAD implantation. The diagnosis of PH is based on pulmonary hemodynamic criteria obtained via right heart catheterization (RHC), i.e., mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg at rest.

1.2 Epidemiology

Over the last several years, LVADs have become a more frequent treatment choice for patients with end-stage HF. This is due to the improvement in the engineering design and reduction in size of these devices. For example, the US-based Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has over 12,000 LVADs in their database, of which 6000 were implanted since 2012 [Kirklin 2014].

While LVADs improve left-sided hemodynamic variables (e.g., increase cardiac output [CO], reduce pulmonary artery wedge pressure [PAWP]), RVF occurring after the

implantation of LVADs is a major cause of morbidity and mortality [Patlolla 2013, Grant 2012, Kukucka 2011b, Kormos 2010]. The incidence of RVF ranges from 9–44%, depending on the definition of RVF used, the type of device used (pulsatile or continuous flow), the indication for LVAD support (bridge to transplantation, bridge to recovery, or DT) and finally, the baseline characteristics or comorbidities of the studied population [Patlolla 2013].

1.3 Current management

The management of PH post-LVAD implantation starts with measures to prevent RVF in the preoperative period. Preoperatively, identifying high-risk patients, choosing the optimal timing of implanting an LVAD and consideration of total artificial heart or initial biventricular assist device are imperative. Intraoperatively, interventions for RVF management include short-term right heart bypass, implantation of a temporary right ventricular assist device (RVAD) and inhaled pulmonary vasodilators. Post-operatively, the management of PH complicated with RVF in these patients includes the use of pulmonary vasodilators, changing the pump speed under echocardiography guidance and if refractory RVF, consideration of an RVAD implantation [Patlolla 2013].

To date, the role of pulmonary vasodilators in LVAD patients with PH has only been investigated in small pilot studies. Inhaled nitric oxide (iNO) decreased pulmonary arterial pressures and improved LVAD flow in a study in which 11 LVAD patients received inhaled iNO at 20 ppm post-operatively [Argenziano 1998]. These results, however, were not reproduced in two small studies in which LVAD patients were given iNO at 40 ppm intra- and post-operatively [Kukucka 2011a, Potapov 2011]. Antoniou et al examined the use of iloprost in 7 patients with right ventricular dysfunction post-LVAD insertion treated simultaneously with inotropes and iNO [Antoniou 2012]. The authors reported a significant reduction in PVR, mPAP, PAWP, and an increase in LVAD flow post-combined inhaled therapy.

In an open-label study of 26 LVAD recipients, sildenafil therapy plus LVAD support was more effective than LVAD alone in lowering PVR [Tedford 2008]. Specifically, the average PVR in the sildenafil-treated group fell from 5.9 to 3 Wood units (WU) while the PVR in the LVAD recipients not receiving sildenafil was reduced by less than 1 WU. Klodell et al also investigated the role of sildenafil in LVAD patients with persistent PH [Klodell 2007]. In 10 patients on inotropic therapy with dobutamine and milrinone, sildenafil administration produced a significant reduction in systolic PAP within 90 min of oral administration.

A case report published by Imamura et al reported on the effects of bosentan in a case of persistent PH post-implantation of a continuous-flow LVAD resulting in significantly decreased PVR [Imamura 2013]. LaRue et al investigated 50 patients on bosentan in a

single center series; treated for a mean duration of 16.3 (± 12.1) months, including 30 patients for greater than 1 year [LaRue 2013]. The study results showed the drug to be well tolerated in this patient cohort. In addition, at 6-month follow-up there was right-sided decongestion with improvement in both the bilirubin and alkaline phosphatase levels. These studies were replicated in a follow-up single center retrospective study by LaRue [LaRue 2013]. In this cohort, consecutive patients with mean PA > 25 mmHg were treated with bosentan after LVAD implantation for a mean duration of 15.7 (± 12.4) months. Comparison of the baseline to 6-month follow-up data revealed laboratory evidence of decreased BNP, hepatic decongestion as well as improvement in echo-derived pulmonary hemodynamics including PVR decrease of 1.4 WU. Ten patients discontinued the drug for possible side effects, including 3 for liver function test (LFT) abnormalities [LaRue 2013].

The current International Society for Heart and Lung Transplantation guidelines on mechanical circulatory support [Feldman 2013] suggest PH-specific therapies for patients with persistent PH who exhibit signs of right ventricular dysfunction in the non-intensive care unit post-operative period (Class IIb, Level of Evidence C).

1.4 Endothelin-1 and pulmonary hypertension

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 2 distinct receptors for ET-1: endothelin receptor A (ET_A) and endothelin receptor B (ET_B). The 2 receptors have unique binding locations and affinities for the endothelin peptide [Benigni 1995, Massaki 1998]. The ET_A receptors are expressed on pulmonary vascular smooth muscle cells, whereas ET_B receptors are present both on pulmonary vascular endothelial cells and on smooth muscle cells.

When activated, the ET_A receptors located in pulmonary vascular smooth muscle cells mediate a potent vasoconstrictive response, and ET_B 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 ET_A and ET_B receptors mediate the mitogenic action of ET-1 [Clarke 1989, Chua 1992, Davie 2002, Sugawara 1996].

Laboratory and clinical investigations have clearly shown that ET-1 is overexpressed in several forms of pulmonary vascular disease. ET-1 is likely a major factor 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].

1.5 Macitentan

Macitentan is approved in the US, EEA, Canada, Australia, Switzerland, Japan, and additional countries in the Middle East, Asia and Latin America for the treatment of pulmonary arterial hypertension (PAH).

1.5.1 Nonclinical results

Macitentan is an orally active, non-peptide, potent dual ET_A and ET_B antagonist. Macitentan showed dose-dependent efficacy in nonclinical models of hypertension and PH, and is approximately 10 times more potent than bosentan (Tracleer®). In nonclinical safety studies, no effects on normal physiological functions or electrocardiogram variables, including cardiac repolarization, were observed – with the exception of a decrease in arterial blood pressure (BP) observed in a cardiovascular study in dogs. Macitentan has no genotoxic potential. In the pivotal 26-week and 39-week toxicity studies, the exposures in animals at the no-observed-adverse-effect levels were above the anticipated clinical exposures and provided a margin of safety for studies in humans. A study conducted in hairless rats showed that macitentan is not phototoxic *in vivo*. Macitentan does not bind relevantly to melanin. Reproductive toxicity studies showed that macitentan is teratogenic without affecting male or female fertility. Teratogenicity is considered to be an endothelin receptor antagonist (ERA) class effect.

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

1.5.2 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].

1.5.3 Phase 2 results

Phase 2 studies were conducted in patients with mild-to-moderate essential hypertension, and in patients with idiopathic pulmonary fibrosis (IPF).

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 (vs. placebo) from baseline to Week 8 in mean sitting diastolic blood pressure (DBP) at trough, which was the primary endpoint of the study.

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.

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

1.5.4 Phase 3 efficacy results in PAH

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] [Appendix 1]. 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 (36%) or in combination with phosphodiesterase-5 (PDE5) inhibitors (61%) or inhaled/oral prostanoids (5%).

The trial demonstrated that macitentan 10 mg reduces the risk of morbidity/ mortality in patients with symptomatic PAH by 45% as compared to placebo of (hazard ratio 0.547, 97.5% confidence limits (CLs) 0.392–0.762, $p < 0.0001$).

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. Additionally, improvements in WHO FC from baseline to Month 6 were reported for 22.3% of patients in the macitentan 10 mg group, compared to 12.9% of patients in the placebo group. This translates into a 74% higher chance relative to placebo of WHO FC improvement in patients on the 10 mg dose (relative risk 1.74, 97.5% CLs 1.10, 2.74, $p = 0.0063$). The treatment effect of macitentan on WHO FC was maintained over time.

The median change versus placebo in NT-proBNP from baseline to Month 6 was –160 fmol/mL (97.5% CLs –235, –95) with macitentan 10 mg. In a hemodynamic substudy, the observed placebo-corrected treatment effect of reduction in PVR after 6 months of treatment with macitentan 10 mg was 36.5% (97.5% CLs 21.7, 49.2), The placebo-corrected median change in cardiac index (CI) (L/min/m^2) from baseline to Month 6 was 0.58 (97.5% CLs 0.28, 0.93) in the macitentan 10 mg group.

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

1.5.5 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 three placebo-controlled studies with macitentan (two Phase 2 studies in essential hypertension and IPF and one Phase 3 study in PAH), 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. Additionally, cases with ALT/AST > 3 × ULN and total bilirubin > 2 × ULN, suggesting Hy's Law, were reported with very similar incidences across macitentan and placebo treatment groups. All of these events were characterized by confounding factors; linked to the underlying disease or to concomitant disease or medications. Overall, these findings do not indicate that macitentan is associated with a definite hepatotoxicity signal. Patients with serum AST and/or ALT > 3 × ULN are excluded from the study, and monthly liver tests are mandatory during the study.

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 < 8.5 g/dL and who do not recover during the Screening period are excluded from the study. Monthly hemoglobin tests are mandatory during the study.

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 serious adverse events (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.

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 disorders 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, especially 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.

Macitentan has not been studied in PH post-LVAD implantation. Thus, a number of safeguards have been implemented in the current protocol, i.e., monthly follow-up of patients and ongoing safety and efficacy data review by an Independent Data Monitoring Committee (IDMC).

For detailed information on the efficacy and safety profile of macitentan in PAH and other indications, please refer to the most recent version of the macitentan IB [Macitentan IB].

It is the investigator's responsibility to monitor the benefit-risk ratio of study treatment administration, as well as the degree of distress caused by study procedures on an

individual subject level, and to discontinue study treatment or the study if, on balance, he/she believes that continuation would be detrimental to the subjects' well-being.

1.6 Purpose and rationale of the study

PH after LVAD implantation is associated with a worse prognosis. To date, no targeted PAH therapy has demonstrated efficacy and safety in this patient population in a randomized, placebo-controlled clinical trial. The patients are managed on a day-to-day basis with commercially available PAH medications including PDE5 inhibitors, ERAs, iNO and prostanoids. Use of these pulmonary vasodilators has been mostly based on evidence from single-center, open-label experiences. Specifically, iNO and iloprost have been shown to reduce PVR and right ventricular dysfunction in the perioperative setting, while data from small, uncontrolled studies suggest utility of bosentan and sildenafil as long-term therapy in reducing PVR, thus reducing risk of RVF [Argenziano 1998, Antoniou 2012].

Macitentan is an ERA, currently approved for the treatment of PAH in the US. In the Phase 3 AC-055-302/SERAPHIN study, macitentan demonstrated efficacy in PAH by improving long-term clinical outcomes, functional status and exercise capacity. Based on the aforementioned results with sildenafil and bosentan in PH after LVAD implantation, it is believed that macitentan could be an efficacious treatment for this patient population.

The purpose of this study is to investigate the effect of macitentan on cardiopulmonary hemodynamics as well as the safety and tolerability in patients with PH post-LVAD implantation in a randomized, placebo-controlled study setting.

2 STUDY OBJECTIVES

2.1 Primary objective(s)

To evaluate the effect of macitentan 10 mg on PVR as compared to placebo in subjects with PH after LVAD implantation.

2.2 Secondary objectives

To evaluate the effect of macitentan 10 mg as compared to placebo on cardio-pulmonary hemodynamics and disease severity in subjects with PH after LVAD implantation.

To evaluate the safety and tolerability of macitentan 10 mg in subjects with PH after LVAD implantation.

2.3 Exploratory objectives

To explore the potential effect of macitentan 10 mg as compared to placebo on right ventricular function in subjects with PH after LVAD implantation.

To explore the potential effect of macitentan 10 mg as compared to placebo on selected clinical events in subjects with PH after LVAD implantation.

To explore the potential effect of macitentan 10 mg as compared to placebo on renal function as measured by glomerular filtration rate (GFR) in subjects with PH after LVAD implantation.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This study is designed as a prospective, double-blind, placebo-controlled, multicenter, parallel-group Phase 2 study assessing the efficacy and safety of macitentan in PH post-LVAD implantation.

Approximately 78 adult subjects with PH post-LVAD implantation will be randomized (1:1) to receive either macitentan 10 mg, or matching placebo, once daily orally. The attrition rate is expected to be 10%, leaving 70 evaluable patients at Week 12.

After implantation of the LVAD, subjects must meet Baseline hemodynamic criteria of PH via RHC during the last measurement prior to the first dose of study treatment, defined as mPAP $\geq$ 25 mmHg at rest *and* PAWP $\leq$ 18 mmHg *and* PVR > 3 WU. Patients must be randomized within 90 days of surgical implantation of LVAD and within 14 days of Baseline RHC.

Patients must be considered stable for 48 h prior to the Baseline RHC. Stability is defined as having no LVAD pump speed/flow rate changes, being on a stable dose of oral diuretics, receiving no intravenous (i.v.) inotropes or vasopressors, and being able to ambulate, for 48 h prior to the Baseline RHC.

The study will be conducted in approximately 50 clinical sites in the US. Randomization will proceed until the required number of subjects has been reached. Enrollment will be competitive across participating sites. Actelion may replace sites with no study subject enrollment. The planned study duration is approximately 36 months from first subject, first visit to last subject, last visit.

The study consists of the following study periods:

Screening period: Commences immediately following LVAD implantation and ends with subject Randomization (up to a maximum of 90 days after surgical implantation of

LVAD). The Screening visit is the date at which signature on the Informed Consent Form (ICF) is obtained prior to initiation of any study-mandated procedures. Screening and Randomization visits may be conducted on the same day provided that eligibility is confirmed and all study-mandated procedures are completed prior to Randomization.

Treatment period: Study treatment is defined as the dosing (intake) by the subject of double-blind study drug (macitentan or placebo). The treatment period starts immediately after Randomization with the first dose of study drug at the end of Visit 2 (Day 1 of study) and ends with EOT on the day of the last dose of study drug (scheduled Day 84, Week 12), or earlier in case of premature discontinuation of study treatment.

Subjects who prematurely discontinue study treatment must have an EOT visit within 7 days of study treatment discontinuation.

Post-treatment safety follow-up period: Subjects who complete the study treatment as planned, i.e., a full 12-week study period, and those who prematurely discontinue study treatment, will enter a 30-day safety follow-up period, which ends with the End-of-Study (EOS) visit at least 30 days after the permanent discontinuation of study treatment.

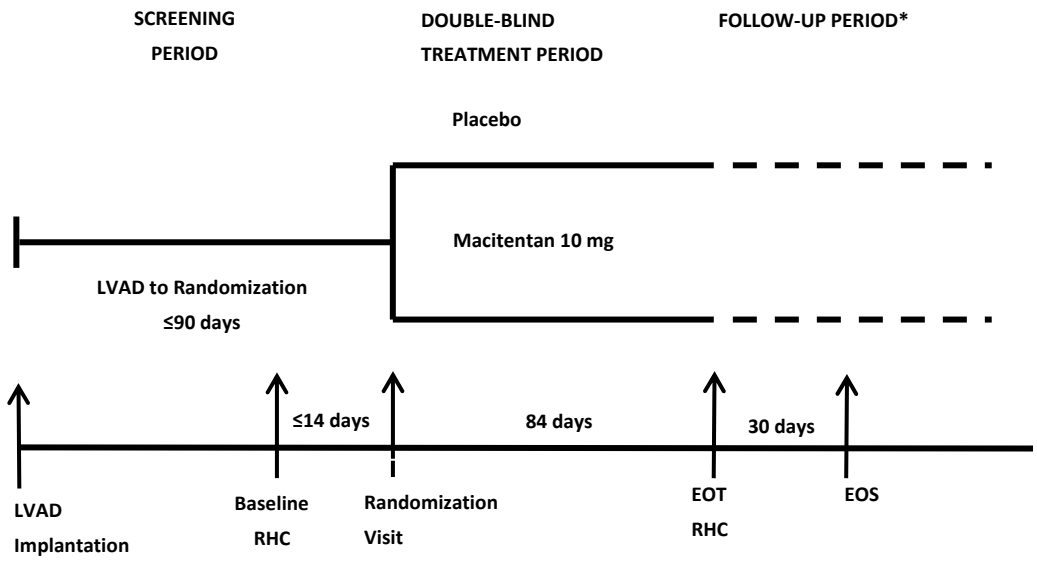
In addition, Unscheduled Visits may also take place during the treatment and follow-up periods [see Table 1].

For an individual subject, the study has ended once the EOT has been performed and the 30-day safety follow-up is complete (EOS).

The study is considered complete when all subjects have ended as detailed above.

Study Duration: Subject participation in the study will be up to 90 days (Screening period) + 12 weeks (double-blinded treatment period) + 30 days (safety follow-up period). The overall study design is depicted in Figure 1.

Figure 1 Study design



***** Subjects who complete the study as planned, i.e., full 12-week study period and those who prematurely discontinue study treatment will enter a 30-day safety follow-up period, which ends with the EOS visit at least 30 days after the permanent discontinuation of study treatment.
EOT = End-of-Treatment; EOS = End-of-Study, LVAD = left ventricular assist device; RHC = right heart catheterization.

3.2 Study design rationale

A placebo-controlled trial conducted in a randomized, double-blind fashion provides the most definite and rigorous method of evaluating the efficacy and safety of a medical treatment.

The present study aims at assessing whether macitentan improves hemodynamic variables, and whether this improvement would translate into functional improvement in subjects with PH post-LVAD implantation. The study also assesses the safety of macitentan in this patient population. Subjects will receive macitentan or placebo for 12 weeks followed by a 30-day safety follow-up. The 12-week double-blind treatment period is selected because it is considered to be adequate to observe the anticipated treatment effect on the primary endpoint of change in PVR, but short enough to minimize risk of Randomization to placebo. The number of missing assessments due to premature study discontinuation is also expected to be minimized. The lack of an appropriate control arm in the previous small trials that tested pulmonary vasodilators in the post-LVAD implantation population is a limitation. Such limitation stems from the inability to differentiate between the mechanical unloading effects of the LVAD, and at

times of concomitant therapies such as inotropes and iNO, from the pharmacologic pulmonary vasodilatory properties of the individual agent being examined. Additionally, in studies involving hemodynamics, variability and placebo effect are of sufficient magnitude to justify the inclusion of a placebo control group [Wright 2009]. Most importantly, HF patients with "fixed" PH have been reported to demonstrate a marked reduction in pulmonary pressures at 6 months with LVAD therapy alone [Mikus 2011], which strongly suggests that a placebo arm is greatly needed to capture the true effects of the study drug rather than those of the LVAD itself. As most of the benefit from pulmonary vasodilators is likely to exist in patients with persistently elevated PVR and/or RV dysfunction after LVAD implantation, the need exists to evaluate post-LVAD hemodynamics for appropriate patient selection [LaRue 2015]. Hence, the present study aims to utilize post-LVAD hemodynamics as Baseline variables for a planned comparison with 12-week hemodynamics.

Treatment with ERAs has been associated with increased incidence of edema, anemia and/or decreased hemoglobin as well as LFT abnormalities. From three placebo-controlled studies with macitentan, involving 863 patients on macitentan and 370 patients on placebo, no significant imbalance in LFT elevations was observed across macitentan treatment groups (any dose) and placebo. However, due to the underlying disease in this patient population that increases the likelihood of safety events, a placebo arm is the only definitive way to draw (or rule out) an association between the use of the study treatment and those potential safety events.

3.3 Study committees

A Steering Committee has been appointed by Actelion to contribute to the design of the protocol, oversee the conduct of the study, evaluate the results, and support publications. The committee is governed by a Steering Committee charter.

An IDMC with members representing the specialties of cardiology and biostatistics, has overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data from the study and may recommend modification, discontinuation or completion of the study, thus ensuring that the study is being conducted with the highest scientific and ethical standards. The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter.

A Clinical Event Committee (CEC) has been appointed by Actelion to review data on hospital admission for HF and death due to any cause (in a blinded fashion), so as to allow for a standardized assessment of HF admission events, limiting variability and potential biases associated with site-based event(s). The Committee is governed by a Clinical Endpoints Committee charter.

A Core Hemodynamics Laboratory (CHL) has been appointed by Actelion to review RHC tracings, so as to allow for a standardized assessment of data quality. The RHC tracings data will be recorded by the CHL in a CHL eCRF, entered into the study database, and analyzed for variability. Services of the CHL will be governed by a charter.

4 SUBJECT POPULATION

4.1 Subject population description

Subjects enrolled will be male or female aged 18 years and over, and meeting the hemodynamic criteria of PH post-LVAD implantation. Patients must be considered clinically stable.

4.2 Rationale for the selection of the study population

The primary objective of the study is to demonstrate a reduction in PVR versus Baseline with macitentan treatment as compared to placebo. Thus, patients need to present with elevated PVR (> 3 WU). Patients need to present with PAWP ≤ 18 mmHg to rule out that their elevated PVR and mPAP is due to left-sided dysfunction.

The absence of restriction on WHO FC and 6MWD will permit patients with severely symptomatic PH to be enrolled.

Patients with hemoglobin < 8.5 g/dL, or AST and/or ALT > 3 × ULN, and who do not recover during the Screening period are excluded. Such patients are at increased risk of premature discontinuation and would impact on the study's ability to achieve its primary objective [see Section 1.5.5].

As there is limited data on macitentan in pediatric PAH, subjects under the age of 18 years are excluded.

4.3 Inclusion criteria

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

1. Written Informed Consent prior to initiation of any study-mandated procedure(s).
2. Males or females ≥ 18 years of age.
3. Surgical implantation of LVAD within 90 days prior to Randomization.
4. Hemodynamic evidence of PH on Baseline RHC by the thermodilution method. Baseline RHC is defined as the last hemodynamic measurements after LVAD implantation and prior the first dose of study treatment. PH is defined as:
    a. mPAP ≥ 25 mmHg *and*
    b. PAWP ≤ 18 mmHg *and*
    c. PVR > 3 WU.

5. Stabilization of the patient for 48 h prior to the Baseline RHC, defined as:
    a. No LVAD pump speed/flow rate changes *and*
    b. Stable dose of oral diuretics *and*
    c. No i.v. inotropes or vasopressors *and*
    d. Patient able to ambulate.
6. A woman of childbearing potential [see definition in Section 4.5.1] is eligible *only* if the following applies:
    a. A negative serum pregnancy test result during the Screening period (Visit 1) and Randomization (Visit 2) *and*
    b. Agreement to undertake monthly serum pregnancy tests during the study and up to 30 days after study treatment discontinuation *and*
    c. Agreement to use one of the methods of contraception / follow the contraception scheme described in Section 4.5 from Screening and up to *at least 30 days after* study treatment discontinuation.
7. Patient must be randomized within 14 days of Baseline RHC.

4.4 Exclusion criteria

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

1. Documented severe obstructive lung disease defined as: forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC) < 0.7 associated with FEV_1 < 50% of predicted value after bronchodilator administration.
2. Documented moderate to severe restrictive lung disease defined as: total lung capacity < 60% of predicted value.
3. Documented pulmonary veno-occlusive disease.
4. Patients undergoing dialysis.
5. Hemoglobin < 8.5 g/dL at Randomization.
6. AST or ALT > 3 × ULN at Randomization.
7. Severe hepatic impairment, e.g., Child-Pugh Class C liver disease.
8. Body weight < 40 kg at Randomization.
9. Doppler mean blood pressure < 65 mmHg at Randomization.
10. GFR < 30 mL/min at Randomization.
11. Pregnant, planning to become pregnant during the study period, or breastfeeding.
12. Treatment with ERAs, PDE5 inhibitors, i.v., subcutaneous (s.c.) or oral prostanoids, or guanylate cyclase stimulators within 7 days prior to Baseline RHC or study treatment initiation.
13. Treatment with inhaled prostanoids (e.g., iloprost, epoprostenol) or nitric oxide within 24 h prior to Baseline RHC or study treatment initiation.

14. Treatment with strong inducers of cytochrome P450 isozyme 3A4 (CYP3A4) within 28 days prior to study treatment initiation (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort).
15. Treatment with strong inhibitors of CYP3A4 within 28 days prior to study initiation (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, saquinavir, boceprevir, telaprevir, iopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, and idinavir).
16. Treatment with another investigational drug (planned, or taken) within 28 days prior to study treatment initiation.
17. Known hypersensitivity to ERAs, or to any of the study treatment excipients.
18. Any condition that prevents compliance with the protocol or adherence to therapy.
19. Known concomitant life-threatening disease with a life expectancy < 12 months.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

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

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Premature ovarian failure confirmed by a specialist.
- Pre-pubescence[2], XY genotype, Turner syndrome, uterine agenesis.
- Post-menopausal, defined as 12 consecutive months with no menses without an alternative medical cause (International Council for Harmonisation [ICH] M3 definition).

[2] Childbearing potential status and pregnancy status will be assessed at each visit and recorded in the electronic case report form (eCRF).

4.5.2 Acceptable methods of contraception

Women of childbearing potential must use a reliable method of contraception. The use of one of the following options is regarded as reliable contraception:

Option 1

One method from this list:
Standard intrauterine device (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

4.6 Medical history

Relevant medical history either previous to or ongoing at time of Randomization (Visit 2), as defined below, must be recorded in the eCRF:

- Chronic medical conditions and acute medical conditions within the past 6 months (e.g., anemia, hepatitis C infection, HIV infection, obstructive or restrictive lung disease, hypertension, renal disease)
- Any previous life-threatening conditions, including date (e.g., myocardial infarction).

5 TREATMENTS

5.1 Study treatment

Treatment in this study is double-blind, and comprises investigational treatment (i.e., active drug macitentan) or matching placebo administered orally once daily. Up- or down-titration does not apply.

5.1.1 Investigational treatment: description and rationale

The investigational treatment is macitentan at the approved dose for PAH of 10 mg and is administered orally and at a frequency of once daily.

5.1.2 Comparator(s) and/or matching placebo: description and rationale

Matching placebo is administered orally and also once daily. Rationale for the use of a placebo arm is provided in Section 3.2.

5.1.3 Study treatment administration

The first administration of study treatment will take place at the clinical site during Randomization (Visit 2), and only after: successful completion of the ICF procedure, completion of all Screening/Randomization assessments, and confirmation that the patient meets all study eligibility criteria.

Thereafter, one tablet (macitentan 10 mg or matching placebo) must be taken orally every morning irrespective of food intake. If a morning dose is missed, the next dose must be taken at the next scheduled morning time point (i.e., do not take one tablet in the evening and then one tablet the next morning). Two tablets must never be taken on the same day.

At all subsequent visits, study treatment must be taken before any study procedures are performed. If a dose is not taken in the morning prior to arrival for the clinic visit, the next dose can be administered at the time of the clinic visit and prior to any study-related assessments.

5.1.4 Treatment assignment

Eligible subjects will be randomized in a 1:1 ratio to either macitentan 10 mg or matching placebo. At Visit 1 (Screening), all screened subjects will be assigned a study-specific subject number by the Interactive Voice/Web Response System (IxRS) provider. Details are provided in the IxRS manual. At Visit 2 (Randomization), and after having confirmed the eligibility of the subject and prior to the start of study treatment, the investigator/delegate contacts the IxRS to randomize the subject. The IxRS assigns a Randomization number to the subject, and assigns the treatment bottle number which matches the treatment arm assigned by the Randomization list to the Randomization number. The bottle with this unique number is then dispensed to the subject and the first dose is administered.

The Randomization list is generated by an independent Contract Research Organization (CRO) and kept strictly confidential.

5.1.5 Blinding

This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, Actelion and CRO staff involved in the conduct of the study will remain blinded to the treatment until study closure.

Until the time of unblinding for final data analysis, the Randomization list is kept strictly confidential, and accessible only to authorized persons who are not involved in the conduct of the study. The Randomization code will be provided to the independent statistical analysis center of the IDMC.

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

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full Randomization information will be made available for internal Actelion data analysis only after database closure, and in accordance with Actelion standard operating procedures (SOPs).

5.1.6.2 Unblinding

The IDMC has overall responsibility for safeguarding the interests of subjects by monitoring data from the study and may recommend modification, discontinuation or completion of the study. The process for IDMC review of unblinded data is defined in the IDMC charter.

5.1.6.3 Unblinding for SUSARs

When a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The Randomization code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information will be anonymized and provided to Actelion Global Drug Safety, respective health authorities and Institutional Review Boards / Independent Ethics Committees (IRBs/IECs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.4 Emergency procedure for unblinding

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

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

The circumstances leading to the code break must be documented in the site study file and eCRF.

5.1.7 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.

5.1.7.1 Study treatment packaging and labeling

5.1.7.1.1 Study treatment packaging

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

5.1.7.1.2 Study treatment labeling

Study treatment is labeled to comply with the applicable US laws and regulations. Each medication bottle has a label with a tear-off part specifying the study protocol number, the packaging batch number, and the bottle number. When the study treatment is given to the subject, this tear-off part must be removed and attached to the Study Treatment Dispensing Log.

5.1.7.2 Study treatment distribution and storage

Treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the medication labels. The investigator is responsible for the safe and proper handling and storage at the investigational site and that the study treatment is administered only to patients enrolled in the study and in accordance with the protocol.

5.1.7.2.1 Study treatment distribution

The study centers will be supplied with study treatment according to the centers' needs, depending on the rate of subject enrollment. Each center will have an individual stock of study treatment, which will be re-supplied continuously as soon as a predefined minimum level of study treatment has been reached.

5.1.7.2.2 Study treatment storage

Study treatment 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 (DoA) form.

The subject must be educated on the proper study treatment storage conditions at home.

The study treatment must be stored below 30 °C (86 °F). Keep the bottle tightly closed to protect from moisture. Unopened, sealed medication bottles may be stored in the refrigerator (above +2 ºC [36 ºF]). Storage below +2 ºC [36 ºF] (e.g., in the freezer) **is not permitted**. Opened bottles of study drug **must not** be stored in the refrigerator or freezer.

A temperature log must be maintained and temperature control should occur at least on a weekly basis at the site. Actelion will provide a temperature log; 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 site is acceptable as long as all required information is included and certification of calibration is provided. If the temperature is captured electronically, a print-out should be made available to the clinical research associate (CRA) during each on-site visit for filing in the investigator site file (ISF).

If a deviation from the defined temperature range is identified by the study center, the deviation must be reported to the CRA, preferably in writing and with supporting documentation (e.g., copy of the temperature log showing data for all excursion days). The CRA should immediately contact Actelion for further advice. The affected study treatment will not be used (e.g., it will be segregated physically at the study center) until confirmation from Actelion is obtained that its use is safe. If the temperature deviation is outside of the acceptable limit, the study treatment is kept segregated at the study center, and returned to Actelion following internal study treatment return processes. New study treatment supplies will be provided to the study center.

Site temperature deviations correspondence must be kept in the ISF.

5.1.7.3 Study treatment dispensing

Study treatment can only be dispensed by an authorized study investigator or delegate listed on the DoA form.

The subjects will receive the study treatment (one childproof bottle containing 36 tablets each) at Visit 2 (Randomization), Visit 3 (Week 4), and Visit 4 (Week 8) to cover the treatment period up to the EOT (Week 12) visit. Subjects are asked to return all used, partially used, and unused study treatment bottles at the Week 4, 8, and 12 visits.

The protocol-mandated study treatment dispensing/return procedures may not be altered without prior written approval from Actelion. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

Once a subject has been randomized and study treatment assigned, the corresponding bottle must not be used for another subject. If a subject has been dispensed a bottle in error (one that has not been allocated yet to another subject), the IxRS helpdesk and study monitor / CRA must immediately be contacted.

At the time study treatment is distributed, the subject should be educated on the proper timing of dosing and the proper storage conditions of study treatment at home [see Section 5.1.7.2.2].

5.1.7.4 Study treatment return and destruction

The site must record the amount of study treatment received, dispensed, used, lost and returned during the study.

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused study treatment bottles, which will be sent to the warehouse, where Actelion or a sponsor delegate will check treatment reconciliation. In certain circumstances, used and unused treatment bottles may be destroyed at the site once treatment accountability is

finalized and has been checked by Actelion or their delegate, and written permission for destruction has been obtained from Actelion.

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

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

- Dispensed bottle number
- Date dispensed / number of tablets dispensed
- Date returned / number of tablets returned.

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

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

5.1.8.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability, as per formula below:

Compliance = [(number of tablets provided to subject - number of tablets returned) / total number of tablets that should have been taken during the period] × 100

During the study, and at each visit, compliance is expected to be between 80% and 120%. The investigator must check the reasons for any non-compliance with the subject and discuss actions to be taken to avoid re-occurrence at the next visit.

5.1.9 Study treatment dose adjustments and interruptions

Study treatment may be temporarily interrupted only 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 5.1.11.

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

Interruptions of study treatment should be kept as short as possible. If treatment is stopped for more than 14 consecutive days, reintroduction is not permitted and treatment must be permanently discontinued [see Section 5.1.11].

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

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Actelion. The main reason, and whether discontinuation of study treatment is the decision of the subject, the investigator, or Actelion, must be documented in the eCRF.

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

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

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

A subject's prior enrollment in an LVAD device study does not constitute eligibility failure. Additionally, simultaneous observational or non-interventional clinical trials (limited to blood sample collection) do not constitute basis for premature discontinuation of study treatment.

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

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study, and will be followed up until EOS or 30 days after study treatment discontinuation, provided that the subject's consent for this limited participation in the study has not been withdrawn.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study.

Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study are described in Section 9.2 and Section 9.4, respectively.

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

A) Pregnancy

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

B) Liver aminotransferases abnormalities

For abnormal laboratory results early in the study's Screening period (e.g., high ALT or AST), the patient should be monitored, provided with appropriate treatment, and reassessed throughout the Screening period (90 days from LVAD implantation) for eligibility.

Interruption of study treatment
Study treatment must be interrupted in the following cases:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and $\leq 8 \times$ 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, aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must continue to be monitored 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 2 consecutive weeks; longer interruptions must lead to permanent discontinuation of study treatment.

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. Local laboratories can be used for determination of subject status. However, a central laboratory specimen must also be collected and submitted prior to reintroduction of study treatment.

Liver aminotransferase levels must then be checked within 3 days after reintroduction, again after a further 2 weeks, and thereafter according to the recommendations above (i.e., at monthly intervals). Specimens should be collected and submitted to the central laboratory as Unscheduled Visits.

Permanent discontinuation of study treatment

Study treatment 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, 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 treatment discontinuation until values return to pre-treatment levels, or within normal ranges.

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

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

C) Hemoglobin abnormalities

For abnormal laboratory results early in the study's Screening period (e.g. low hemoglobin), the patient should be monitored, appropriate treatment provided, and reassessed throughout the Screening period (90 days from LVAD implantation) for eligibility.

In case of hemoglobin decrease from Baseline* of > 2.0 g/dL, a re-test must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

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

Study treatment 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 < 6.5 g/dL,
- A decrease in hemoglobin from Baseline* of > 5.0 g/dL,

- 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 or if it returns to a value close to that at Baseline.

Interruption of study medication must not last longer than 2 consecutive weeks; longer interruption must lead to permanent discontinuation of study treatment.

Local laboratories can be used for determination of subject status. However, a central laboratory specimen must also be collected and submitted prior to reintroduction of study treatment.

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

D) Initiation of a prohibited concomitant medication

Study treatment must be permanently discontinued if a prohibited concomitant medication is initiated. Prohibited concomitant medications are listed in Section 5.2.4.

E) Clinical evidence of worsening PH or HF

Study treatment may be discontinued if the study subject demonstrates signs and symptoms of progressive HF reflecting worsening PH and RVF. Examples include, but are not limited to, the need for RV support pharmacologically with inotropes or mechanically with the implantation of RVAD, the development of diuretics resistance, objective evidence of declining RV function on echocardiography, evidence of increased PVR and/or decreased CO on RHC, and the need for escalation of PH therapies (as covered in D). The decision to discontinue the study treatment is based upon the clinical judgment and discretion of the principal investigator (PI) and is not limited to the examples listed above but will be documented in the eCRF.

F) Cardiac transplantation

Study treatment must be permanently discontinued if a subject becomes a recipient of a cardiac transplant. RHC obtained prior to cardiac transplantation, to define the subject candidacy, must be captured as EOT RHC.

In case of premature study treatment discontinuation, all EOT assessments, especially RHC, should be performed as detailed per EOT visit.

5.2 Previous and concomitant therapy

5.2.1 Definitions

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

A therapy that is study-concomitant is any treatment for which the start date is on or after the signing of informed consent or up to 30 days after study treatment discontinuation.

A therapy that is study treatment-concomitant is any treatment for which the start date is on or after the first administration of study treatment up to Week 12 or earlier in case of premature discontinuation of study treatment.

5.2.2 Reporting of previous/concomitant therapy in the eCRF

The use of all concomitant therapy (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous therapy must be recorded in the eCRF if discontinued less than 28 days prior to Randomization. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, and indication will be recorded in the eCRF.

Hormonal contraceptives will be recorded on the contraception page of the eCRF.

5.2.3 Allowed concomitant therapy

Oral or i.v. diuretics are allowed and may be adjusted during the treatment period.

(Treatment with oral diuretics is allowed if ongoing at a stable dose for at least 48 h prior to the Baseline RHC.)

5.2.4 Prohibited concomitant therapy

- PAH-specific therapy (ERAs, i.v., s.c., inhaled or oral prostanoids, PDE5 inhibitors, guanylate cyclase stimulators).
- iNO.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir,saquinavir, boceprevir, telaprevir, iopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, and idinavir) and strong inducers of CYP3A4 (e.g., carbamazepine, rifampicin, rifabutin, phenytoin and St. John's Wort).
- Any investigational drug.

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

5.3 Allowed LVAD flow rate

The LVAD pump speed/flow rate may be adjusted during the treatment period, and during the Baseline RHC.

(The LVAD pump speed/flow rate must be stable for at least 48 h prior to Baseline RHC.)

6 STUDY ENDPOINTS

Baseline is defined as the last value obtained prior to first dose of study treatment.

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is PVR ratio of Week 12 to Baseline. PVR is obtained by the thermodilution method.

6.1.2 Secondary efficacy endpoints

- Change from Baseline to Week 12 in mean right atrial pressure (mRAP), mPAP, PAWP, CI, total pulmonary resistance (TPR), and mixed venous oxygen saturation (SVO_2), all measured at rest.
- Change from Baseline to Week 12 in NT-proBNP.
- Change from Baseline to Week 12 in WHO FC.

6.1.3 Exploratory efficacy endpoints

- Change from Baseline to Week 12 in echocardiographic variables that include:
  - 2D global RV longitudinal strain (global RVLS)
  - RV sphericity index (RVSI)
  - RV end systolic area
  - RV end diastolic area
  - Tricuspid annular plane systolic excursion (TAPSE)
  - Tricuspid peak annular velocity s' (S')
  - RV fractional area change (RVFAC)
  - Tricuspid peak diastolic annular velocities e', a' (E', A')
- Time to first occurrence of clinical events, from enrollment to Week 12. These clinical events include:
  - Hospital admission for HF
  - Re-initiation of i.v. diuretics ≥ 48 h duration
  - Re-initiation of i.v. inotropes ≥ 48 h duration

- Initiation of PDE5 inhibitors
- Need for RVAD / total artificial heart (TAH)
- Need for renal replacement therapy (RRT)
- Death

- Days in the hospital after hospitalization for HF.
- Change in GFR from Baseline to Week 12.

6.2 Safety endpoints

- Treatment-emergent AEs up to 30 days after study treatment discontinuation.
- AEs leading to premature discontinuation of study treatment.
- Death up to 30 days after study treatment discontinuation.
- Treatment-emergent SAEs up to 30 days after study treatment discontinuation.
- Change from Baseline to EOT in vital signs.
- Occurrence of liver function test (ALT and/or AST) abnormality (≥ 3 × ULN; ≥ 3 and < 5 × ULN; ≥ 5 and < 8 × ULN; ≥ 8 × ULN) up to EOT.
- Occurrence of ALT and/or AST abnormality ≥ 3 × ULN associated with bilirubin ≥ 2 × ULN up to EOT.
- Proportion of patients with treatment-emergent hemoglobin abnormality (< 10.0 g/dL, and < 8.0 g/dL) as compared to Baseline up to EOT.
- Treatment-emergent marked laboratory abnormalities up to EOT.

Marked laboratory abnormalities are defined in the central laboratory manual.

6.3 Biomarker endpoints

Change in NT-proBNP will be assessed from Baseline to Week 12 (EOT) as part of the secondary efficacy endpoints analysis [see Section 6.1.2]. Additional circulating biomarkers may be analyzed in an exploratory format (post-hoc) based on available scientific evidence. No genetic testing will be performed.

7 STUDY ASSESSMENTS

All study assessments are performed by a qualified study staff member: medical, nursing, or specialist technical staff, and are recorded in the eCRF, unless otherwise specified. Study assessments performed during Unscheduled Visits will also be recorded in the eCRF. When applicable, the assessments should be performed in the following order:

- Blood sampling
- Physical examination

- WHO FC
- RHC at rest
- Echo (i.e., 3D, 2D, M-mode and Doppler echocardiography)

If the PI delegates any study procedure/assessment for a subject, e.g., RHC, blood sampling etc., to an external facility, he/she should inform Actelion of 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 PI.

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

- Temperature measurement devices for study medication storage area and freezer
- RHC equipment
- Scale for measuring body weight

7.1 Screening/Baseline assessments

Date of informed consent, Baseline demographics (sex, age, race, ethnicity, body weight, height) as well as a reason for why a woman is not considered to be of child-bearing potential (if applicable) are to be recorded in the eCRF at Visit 1 / Screening only after Informed Consent has been signed.

Complete, clinically relevant medical history (previous and ongoing at Randomization) as described in Section 4.6 and disease characteristics, vital signs, body mass index (BMI), and previous/ongoing medications [see Section 5.2.2] are to be documented in the eCRF at Visit 1 / Screening. Historical data of pre-LVAD RHC and non-Baseline post-LVAD RHC may be entered into the eCRF.

A physical examination of the subject should be performed at Visit 1 / Screening and Visit 2 / Randomization. Data are not collected in the eCRF though abnormal findings are to be recorded as AEs.

Reason for Screening failure, if applicable, must be recorded in the eCRF.

Serum laboratory and pregnancy testing should be performed at Visit 1 / Screening and repeated at Visit 2 / Randomization, whereas blood sampling for Baseline NT-proBNP should only be performed at Visit 2 / Randomization.

At Visit 2 / Randomization, WHO FC, vital signs, and body weight is to be assessed and ongoing medications are to be collected in the eCRF. Study medication is dispensed at this visit.

AEs and SAEs occurring during the course of the study are to be documented in the eCRF.

7.2 Efficacy assessments

7.2.1 Hemodynamic measurements - right heart catheterization

Eligibility for the SOPRANO study should be considered for all post-LVAD patients provided they have clinical or hemodynamic evidence of PH (e.g., PVR > 3 WU) on pre-LVAD RHC or immediate post-LVAD hemodynamics. Subjects without clinical or hemodynamic evidence of PH should not be screened for the study.

The patient must be stable for 48 h prior to the Baseline RHC. Stabilization is defined as:

- No LVAD pump speed/flow rate changes, and
- Stable dose of oral diuretics, and
- No i.v. inotropes or vasopressors, and
- Patient able to ambulate.

Baseline RHC is defined as the last hemodynamic measurements after LVAD implantation and prior to first dose of study treatment. Hemodynamic evidence of PH on Baseline RHC is one of the inclusion criteria of SOPRANO. PH is defined as: mPAP ≥ 25 mmHg, PAWP ≤ 18 mmHg and PVR > 3 WU.

An RHC conducted prior to signing the Informed Consent may be accepted as the Baseline RHC. Baseline RHC must be performed by the thermodilution method, after LVAD implantation and prior to first dose of study treatment (which must occur within 90 days post-surgical implantation of LVAD, see Section 3). Randomization (Visit 2) must be within 14 days of Baseline RHC. Patients are excluded if they were treated with ERAs, PDE5 inhibitors, i.v., s.c., or oral prostanoids, or guanylate cyclase stimulators within 7 days prior to Baseline RHC or study treatment initiation. Patients are excluded if they were treated with inhaled prostanoids (e.g., iloprost, epoprostenol), nitric oxide or i.v. inotropes or vasopressors within 24 h prior to Baseline RHC or study treatment initiation. LVAD pump speed/flow rate may be adjusted during the treatment period and during the Baseline RHC.

An RHC is repeated at Week 12, or within 7 days of permanent discontinuation of study treatment if prior to Week 12. The Week 12 RHC must be performed by the thermodilution method, and not within 24 h of treatment with i.v. inotropes or vasopressors.

All RHC procedures must be performed according to the Actelion RHC Instructions. Hemodynamic tracings, and the Hemodynamic Checklist and Data Worksheet (as

provided by Actelion) must be completed and signed by the PI, and filed at site in the subject's file.

The following variables are to be measured and collected in the eCRF: pulse rate, PAWP, mRAP, systolic/diastolic/mean PAP, CO, and SVO_2. Non-invasive mean, SBP and DBP if available, are collected and entered into the eCRF. PVR will be calculated locally and entered into the eCRF. CO measurements, and PVR calculations, during both Baseline and Week 12 RHC must be obtained via the thermodilution method. All primary end point calculations must be based on thermodilution method-calculated PVR.

The following hemodynamic variables will be calculated by Actelion for analysis purposes [see Section 11.2 and the SOPRANO Right Heart Catheterization Instructions for formulae]: PVR, TPR, and CI.

7.2.2 WHO functional class

WHO FC is evaluated at Baseline/Randomization and EOT.

7.2.3 Serum NT-proBNP

A blood sample will be drawn at Randomization (Visit 2) and EOT (Visit 5) for the analysis of serum NT-proBNP.

Serum NT-proBNP samples will be stored frozen at −20 °C (−4 °F) ± 2 °C (± 3.6 °F). A temperature log must be maintained and temperature control should occur at least on a weekly basis. NT-proBNP samples will be processed through the central laboratory and the results will be sent electronically to Actelion on an ongoing basis. Further details regarding blood sampling procedures, collection and shipment of biomarker samples are described in the central laboratory manual.

7.2.4 Echocardiography

Echo (i.e., 3D, 2D, M-mode and Doppler echocardiography) will be performed according to the guidelines detailed in the Actelion Echo image acquisition protocol on Visit 2 / Randomization, which will represent the Baseline measurements and be repeated at the Week 12 visit. Baseline ECHO must occur on the day of Randomization. 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 sent to Actelion:

- 2D RVLS
- RVSI
- RV end systolic area
- RV end diastolic area

- TAPSE
- S'
- RVFAC
- E', A'

7.2.5 Clinical events

Time to first occurrence of clinical events, from enrollment to Week 12 will be recorded. These clinical events include:

- Hospital admission for HF
- Re-initiation of i.v. diuretics ≥ 48 h duration.
- Re-initiation of i.v. inotropes ≥ 48 h duration.
- Initiation of PDE5 inhibitors
- Need for RVAD/TAH
- Need for RRT
- Death

Hospital admissions for HF, as an exploratory endpoint, will be adjudicated by the SOPRANO Steering Committee.

7.2.6 Duration of heart failure hospitalization

Duration of HF hospitalization will be captured as the number of days in the hospital after hospitalization for HF, excluding rehabilitation stay. A hospitalization for HF is defined as a hospitalization in which the principal diagnosis is HF. Hospital admissions for HF, as an exploratory endpoint, will be adjudicated by the SOPRANO Steering Committee.

7.2.7 Glomerular filtration rate

Change in GFR from Baseline to Week 12 will be recorded. GFR will be estimated on the basis of serum creatinine levels. The formula can be found in the central laboratory manual.

7.3 Safety assessments

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

7.3.1 Vital signs

Vital signs (BP, pulse rate) will be measured via Doppler at Screening (Visit 1), Randomization (Visit 2), and EOT (Visit 5), and collected in the eCRF. BP (mean, systolic and diastolic, if available) and pulse rate will be measured in a supine or sitting

position after the subject has rested for at least 5 min. The right or left arm may be used. The same position and arm should be used throughout the trial for an individual subject.

7.3.2 Weight and height

Height will be measured at Visit 1 / Screening. Body weight will be measured at Visit 1 / Screening, Randomization, and EOT.

7.3.3 Physical examination

Physical examination (i.e., inspection, percussion, palpation and auscultation) is to be performed during the Screening period (Visit 1) and EOT. The data are not collected in the eCRF, but clinically relevant findings that are present at the signing of Informed Consent must be recorded on the Medical History eCRF page, while physical examination findings made after the signing of Informed Consent and which meet the definition of an AE [Section 10.1.1] must be recorded by the investigator on the AE page of the eCRF.

7.3.4 Laboratory assessments

7.3.4.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at Unscheduled Visits. Central laboratory data will be automatically transferred from the central laboratory database to Actelion's clinical database.

- For the follow-up of abnormal values such as ALT/AST and/or hemoglobin [see Section 5.1.11] central laboratory specimens must be obtained in parallel with local laboratories for re-test and prior to reintroduction of study treatment.

Local laboratory results will be collected in the following situations:

- In case of missing central laboratory values, any local laboratory values noted as significant are to be recorded in the eCRF, especially local laboratory results related to the diagnostic work-up (i.e., detection, confirmation and/or monitoring) of ALT/AST elevations and hemoglobin decreases. In the event that several local laboratory samples are taken on the same day or if the sample was tested several times, the significance of the 'worst' value (e.g., highest value for ALT/AST, lowest value for hemoglobin) should be reported in the eCRF.

- In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency) where a local laboratory is used for the collection

and analysis of blood samples, the results noted as significant will be entered into the clinical database via dedicated eCRF pages. For local laboratories, the investigator/delegate will provide Actelion with the name, professional degree and *curriculum vitae* (CV) of the laboratory director, 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.

- At the time of Screening, local laboratory results may be used for checking subject eligibility (since central laboratory results would not be available immediately). Central laboratory results should be collected once eligibility is confirmed. Laboratory variables required at Visit 2 are repeated at the central laboratory to be used as the Baseline values for safety laboratory endpoints specified in the protocol. Laboratory certification / reference ranges / laboratory director's CV will be collected by the sponsor for all local laboratories providing data that are entered into the clinical and/or safety databases.

If a central laboratory sample is lost, has deteriorated or cannot be analyzed for whatever 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 the central laboratory manual.

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

The last laboratory sample collected for the study will be analyzed prior to database lock. Laboratory samples will be destroyed within one year of database lock.

7.3.4.2 Laboratory tests

Hematology

Hematology tests will be performed at every visit (Visits 1 to 6) and include:

- Hemoglobin, hematocrit
- Erythrocyte count
- Leukocyte count with differential counts
- Platelet count

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

Clinical chemistry

Clinical chemistry tests will be performed at every visit (Visits 1 to 6) and include:

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

Rules for study treatment interruption in case of liver function abnormalities are provided in Section 5.1.11.

GFR

GFR will be estimated on the basis of serum creatinine levels. The formula can be found in the central laboratory manual.

Pregnancy test

A serum pregnancy test for women of childbearing potential will be provided by the central laboratory and will be performed at Visits 1 to 6 and if pregnancy is suspected during the study. A locally approved test can be used; however, the subject must come to the site for a confirmatory serum pregnancy test to be performed by the central laboratory.

7.4 Biomarker and genetic assessments

Besides NT-proBNP, additional circulating biomarkers such as: interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high sensitivity C-reactive protein (hsCRP), ET-1, galectin-3, growth differentiation factor-15 (GDF-15), interleukin 1 receptor ST2, neutrophil gelatinase-associated lipocalin (NGAL), copeptin, high sensitivity cardiac troponin T (hs-cTnT), Cystatin-C and osteopontin, may be analyzed in an exploratory format (post-hoc) based on available scientific evidence.

The last laboratory sample collected for the study will be analyzed prior to database lock. Laboratory samples will be destroyed within one year of database lock.

8 SCHEDULE OF VISITS

Table 1 provides a summary of all visits and assessments described in the following sections.

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.

If the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a prohibited medication, etc.), patients can be re-screened provided that documented authorization has been received from Actelion. All Screening assessments should then be repeated at the time of re-screening.

8.1 Screening period

8.1.1 Screening (Visit 1)

All Screening assessments must be performed within the 90-day Screening period, beginning with LVAD implantation and prior to Randomization. Historical data of pre-LVAD RHC and non-Baseline post-LVAD RHC may be entered into the eCRF.

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

The date of Informed Consent should be recorded as the date of the Screening visit in IxRS.

Screening and Randomization can occur on the same day, provided that all procedures of Visit 1 are completed before the procedures of Visit 2 are initiated.

Visit 1 includes:

- ICF signature.
- Obtain subject number from IxRS.
- Recording of demographics, Baseline characteristics, and medical history.
- Recording of previous and concomitant medications.
- Physical examination.
- Measurement of vital signs, height and body weight.
- Complete laboratory tests, including pregnancy test for women of childbearing potential.
- Recording of methods of contraception (for females of childbearing potential only) and initiation of protocol-compliant contraception if applicable. The reason why a female is not considered to be of childbearing potential will also be collected in the eCRF.
- RHC (unless the procedure was already performed and would be within 90 days of Randomization, and per the requirements described in Section 7.2.1).
- Recording of AEs and SAEs.

The investigator will check all the inclusion/exclusion criteria and decide on the subject's eligibility for the study. It must be verifiable in the source documents that the subject met each of the inclusion criteria and none of the exclusion criteria. If the subject is a Screen failure and not randomized, the reason for Screen failure is to be documented in the IxRS system and in the eCRF.

8.2 Double-blind study treatment period

8.2.1 Randomization (Visit 2)

Visit 2 corresponds to the start of the treatment period (Day 1 of the study) for subjects that are eligible after all Screening assessments have been performed. It must be within 90 days after LVAD implantation and within 14 days of Baseline RHC.

Visit 2 includes:

- Recording of changes in concomitant medications.
- Measurement of vital signs and body weight.

- Complete laboratory tests, including serum pregnancy test for women of childbearing potential.
- Assessment of methods of contraception (for females of childbearing potential only).
- Blood sample for serum NT-proBNP.
- Blood sample for additional circulating biomarkers such as: IL-6, TNF-α, hsCRP, ET-1, galectin-3, GDF-15, interleukin 1 receptor ST2, NGAL, copeptin, hs-cTnT, Cystatin-C and osteopontin, will be collected and may be analyzed in an exploratory format (post-hoc) based on available scientific evidence.
- WHO FC.
- Echo (i.e., 3D, 2D, M-mode and Doppler echocardiography) will be performed. Those include: TAPSE, S', RVFAC, E', A', global RVLS, RV area and RVSI. Additionally, right and left ventricular echo variables may be analyzed in an exploratory format (post-hoc) based on available scientific evidence. Baseline ECHO must occur on the day of Randomization.
- Recording of AEs/SAEs.

After completion of all Screening and Randomization assessments and confirmation of eligibility (i.e., verification of all entry criteria) by the investigator:

- Randomization via IxRS to obtain Randomization and study treatment bottle number.
- Dispensing of 1 bottle of study treatment [see Section 5.1.7.3].

8.2.2 Week 4 (Visit 3)

Visit 3 is scheduled 4 weeks (± 7 days) after Randomization. Visit 3 includes:

- Recording of changes in concomitant medications.
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential.
- Assessment of methods of contraception (for females of childbearing potential only).
- Recording of AEs and SAEs.
- Dispensing of 1 bottle of study treatment [see Section 5.1.7.3].
- Study medication return; subjects are asked to return all used, partially used, and unused study treatment bottles [see Section 5.1.7.3].

8.2.3 Week 8 (Visit 4)

Visit 4 is scheduled 8 weeks (± 7 days) after Randomization. Visit 4 includes:

- Recording of changes in concomitant medications.
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential.
- Assessment of methods of contraception (for females of childbearing potential only).
- Recording of AEs and SAEs.
- Dispensing of 1 bottle of study treatment [see Section 5.1.7.3].
- Study medication return; subjects are asked to return all used, partially used, and unused study treatment bottles [see Section 5.1.7.3].

8.2.4 End-of-Treatment (Visit 5)

EOT is scheduled 12 weeks (± 7 days) after Randomization, or earlier in case of premature discontinuation of study treatment.

EOT includes:

- Recording of changes in concomitant medications.
- Physical examination.
- Measurement of vital signs and body weight.
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential.
- Assessment of methods of contraception (for females of childbearing potential only).
- RHC.
- Blood sample for serum NT-proBNP.
- Blood sample for additional circulating biomarkers such as: IL-6, TNF-α, hsCRP, ET-1, galectin-3, GDF-15, interleukin 1 receptor ST2, NGAL, copeptin, hs-cTnT, Cystatin-C and osteopontin, will be collected and may be analyzed in an exploratory format (post-hoc) based on available scientific evidence.
- WHO FC.

- Echo (i.e., 3D, 2D, M-mode and Doppler echocardiography) will be performed. Those include: TAPSE, S', RVFAC, E', A', global RVLS, RV area and RVSI. Additionally right and left ventricular echo variables may be analyzed in an exploratory format (post-hoc) based on available scientific evidence.
- Study medication return; subjects are asked to return all used, partially used, and unused study treatment bottles [see Section 5.1.7.3].
- Recording of AEs and SAEs.

8.2.5 End-of-Study (Visit 6)

Subjects who complete the study as planned, i.e., full 12-week study period and those who prematurely discontinue study treatment will enter a 30-day safety follow-up period, which ends with the EOS visit at least 30 days (+ 7 days) after the permanent discontinuation of study treatment (last dose of study drug). EOS includes:

- Recording of changes in concomitant medications.
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential.
- Assessment of methods of contraception (for females of childbearing potential only).
- Recording of AEs and SAEs.

8.2.6 Unscheduled Visits (U1, U2, etc)

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), appropriate assessments [as specified in Table 1] may be performed based on the judgment of the investigator and must be recorded in the eCRF. After an Unscheduled Visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

For an individual subject, the study is considered completed once EOT has been performed and the 30-day safety follow-up is complete (EOS).

The study is considered complete when all subjects have completed as detailed above. The planned study duration is approximately 24 months from first subject, first visit to last subject, last visit.

9.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study, die or are lost to follow-up. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, they believe that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

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

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

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

9.3 Premature termination or suspension of the study

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

If a study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the IRBs/IECs, and 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 subjects, and ensure their appropriate treatment and follow-up, as described in Section 9.2. Actelion may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

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

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

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

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

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

After premature study withdrawal, the investigator must remind the subject that he/she must not use any other investigational treatment in the 30 days following study treatment discontinuation. Female subjects of childbearing potential need to be reminded of the requirement to continue using a reliable method of contraception until 30 days after intake of the last dose of study treatment.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

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

AEs include:

- Exacerbation of a pre-existing disease.

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

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

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

10.1.2 Intensity of adverse events

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

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

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

The three categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

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

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

10.1.3 Relationship to study treatment

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

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

An AE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease.

10.1.5 Reporting of adverse events

All AEs occurring after the signing of Informed Consent and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the eCRF of study AC-055-205.

10.1.6 Follow-up of adverse events

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

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 Serious adverse events

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

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

The following reasons for hospitalization are exempted from being reported:

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

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

10.2.2 Reporting of serious adverse events

All SAEs occurring after the signing of Informed Consent and up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF of study AC-055-205, and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

10.2.3 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit for study AC-055-205 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 by the investigator to be causally related to previous exposure to the study treatment.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to 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 subject, and whether or not this event is considered by the investigator to be related to study treatment.

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

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

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation. The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the Investigator's Brochure [Macitentan IB].

The following events that are expected to occur in patients with PAH/PH 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, HF, hypoxia, palpitations, syncope, collapse, systemic arterial hypotension, and tachycardia. These SAEs must also be reported on AE pages in the eCRF and on an SAE form by the investigator to the Actelion Drug Safety department within 24 h of the investigator's first knowledge of the event.

10.3 Pregnancy

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

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring after the signing of Informed Consent and up to 1 month following study treatment discontinuation 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 to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on an AE page in the eCRF.

10.3.2 Follow-up of pregnancy

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

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

10.4 Study safety monitoring

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

In addition, an IDMC is monitoring data from the study and may recommend modification, discontinuation or completion of the study [see Section 3.3].

11 STATISTICAL METHODS

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

A statistical analysis plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

11.1 Analysis sets

11.1.1 Screened Analysis Set

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

11.1.2 Safety Set

The Safety Set (SS) includes all patients who received at least one dose of study drug in the treatment period.

11.1.3 Full Analysis Set

The Full Analysis Set (FAS) includes all patients randomized.

11.1.4 Modified Full Analysis Set

The modified FAS includes all patients in the FAS that have received at least one dose of study treatment in the treatment period and have a Baseline and at least one post-Baseline PVR measurement.

11.1.5 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 variable. The reasons for excluding patients from the PPS will be fully defined and documented in the SAP.

11.1.6 Usage of the analysis sets

The primary efficacy analysis will be performed on the FAS based on treatment as randomized. Secondary and exploratory efficacy analyses will also be performed on the FAS. Sensitivity analyses will be conducted based on the modified FAS for the primary and selected secondary efficacy endpoints.

Safety analyses related to the double-blind treatment period will be performed on the SS based on treatment as received.

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

11.2 Variables

11.2.1 Primary efficacy variable(s)

The primary efficacy variable is PVR ratio of Week 12 to Baseline. PVR [WU] is calculated as (mPAP − PAWP) / CO.

11.2.2 Secondary efficacy variables

Secondary efficacy variables are changes from Baseline to Week 12, for:

- mRAP (mmHg)
- mPAP (mmHg)
- PAWP (mmHg)
- CI (L/min/m^2), calculated as CO / body surface area (BSA) where BSA (m^2) = 0.007184 × $weight^{0.425}$ (kg) × $height^{0.725}$ (cm)
- TPR (WU), calculated as mPAP / CO
- SVO_2 (%)
- NT-proBNP (pmol/L)
- WHO FC (I–IV).

11.2.3 Exploratory efficacy variables

- Echocardiographic variables including:
  - 2D global RVLS
  - RVSI
  - RV end systolic area
  - RV end diastolic area
  - TAPSE
  - S’
  - RVFAC
  - E’, A.’
- Clinical events including:
  - Hospital admission for HF
  - Re-initiation of i.v. diuretics ≥ 48 h duration
  - Re-initiation of i.v. inotropes ≥ 48 h duration
  - Initiation of PDE5 inhibitors
  - Need for RVAD/TAH
  - Need for RRT
  - Death.
- Days in the hospital after index hospitalization for HF.

- Change in GFR from Baseline to Week 12.

11.2.4 Safety variables

- Treatment-emergent AEs up to 30 days after study treatment discontinuation.
- AEs leading to premature discontinuation of study treatment.
- Death up to 30 days after study treatment discontinuation.
- Treatment-emergent SAEs up to 30 days after study treatment discontinuation.
- Change from Baseline to EOT in vital signs.
- Proportion of patients with treatment-emergent ALT and/or AST abnormalities from Baseline up to EOT, classified as:
  - $\geq 3 \times$ ULN;
  - $\geq 3 \times$ ULN and $< 5 \times$ ULN;
  - $\geq 5 \times$ ULN and $< 8 \times$ ULN;
  - $\geq 8 \times$ ULN.
- Proportion of patients with ALT and/or AST abnormality $\geq 3 \times$ ULN in combination with total bilirubin $\geq 2 \times$ ULN from Baseline up to EOT.
- Proportion of patients with treatment-emergent hemoglobin abnormalities as compared to Baseline up to EOT, classified as:
  - < 8.0 g/dL
  - < 10.0 g/dL.
- Treatment-emergent marked laboratory abnormalities up to EOT.

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

The overall type I error is $\alpha = 0.025$ (one-sided). The type II error is set to 0.20 and the power to 80%.

11.3.2 Analysis of the primary efficacy variable(s)

11.3.2.1 Hypotheses and statistical model

The null hypothesis is that the mean PVR ratio is the same in the macitentan and placebo groups.

The alternative hypothesis is that the mean PVR ratio is lower in the macitentan group as compared to the placebo group.

11.3.2.2 Handling of missing data

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

1. If PAWP is missing both at Baseline and post-Baseline, the treatment group medians will be imputed (based on the FAS).
2. If PAWP is missing either at Baseline or post-Baseline, the patient's available PAWP will be imputed.

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

Baseline: Patients without a Baseline PVR measurement will be excluded from the analyses.

Post-Baseline: In patients with a post-Baseline PVR measurement obtained before Week 12, the last post-Baseline PVR measurement will be carried forward.

If a patient has no post-Baseline PVR measurement, the ratio of Week 12 to Baseline PVR will be imputed using the treatment group median based on the FAS.

Other imputation methods for PVR values will be considered (e.g., multiple imputations) as sensitivity analysis. Details will be specified in the SAP.

11.3.2.3 Main analysis

The primary analysis will be performed on the FAS.

PVR will be summarized by time point and treatment group using descriptive statistics as well as geometric means and coefficients of variation (CVs). The ratio of Week 12 to Baseline PVR will be summarized similarly.

The ratio of Week 12 to Baseline PVR will be log-transformed (base e) and analyzed using an analysis of covariance (ANCOVA) with a factor for treatment group and a covariate for Baseline log PVR (macitentan vs. placebo). The treatment group difference (on log scale) and its 95% CLs will be estimated based on the model. The geometric mean ratio (GMR; macitentan vs. placebo) and its 95% confidence interval will be obtained by exponentiation. The null hypothesis will be rejected if the entire 95% confidence interval is below one.

The treatment effect will be expressed as (GMR−1) × 100%, where a negative value indicates a reduction of PVR in the macitentan group as compared to the placebo group.

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.

11.3.2.4 Supportive/sensitivity analyses

The primary and selected secondary efficacy endpoints will be analyzed on the modified FAS as sensitivity analyses. Details of supportive/sensitivity analyses will be specified in the SAP.

11.3.2.5 Subgroup analyses

Additional subgroup analyses will be specified in the SAP.

11.3.3 Analysis of the secondary efficacy variable(s)

Secondary efficacy analyses will be performed on the FAS at α =0.025 (one-sided) using 95% CLs. No correction for multiple testing will be applied for these analyses.

Changes from Baseline to Week 12 in pressure-volume variables (e.g., mRAP, mPAP, PAWP, CI TPR) and SVO_2 will be summarized and analyzed as described in Section 11.3.2.3, but without the log-transformation.

NT-proBNP will be summarized by time point and treatment group using descriptive statistics as well as geometric means and CVs. The ratio of Week 12 to Baseline NT-proBNP will be summarized similarly. The ratio versus Baseline in NT-proBNP will be log-transformed and analyzed using an ANCOVA with covariates for treatment group and Baseline log NT-proBNP.

WHO FC will be summarized by time point and treatment group 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 covariates for treatment group and WHO FC.

11.3.4 Analysis of the exploratory efficacy variable(s)

Exploratory efficacy analyses will be performed on the FAS at $\alpha = 0.025$ (one-sided) using 95% CLs. No correction for multiple testing will be applied for these analyses.

Echocardiographic variables including TAPSE, S', RVFAC, E', A', RVLS, RV area and RVSI will be summarized by treatment and time point (Baseline, Week 12/EOT) using descriptive statistics (n, mean, SD, median, Q1, Q3, and range). The change from Baseline to Week 12/EOT in these variables will be summarized similarly and analyzed using an ANCOVA with a factor for treatment and covariates Baseline log PVR and

Baseline TAPSE, S', RVFAC, E', A', RVLS, RV area and RVSI, respectively. The adjusted treatment effect and its 95% CI will be presented.

Clinical events including: hospital admission for HF, re-initiation of i.v. diuretics ≥ 48 h, re-initiation of i.v. inotropes ≥ 48 h, need for RVAD/TAH, need for RRT and death will be summarized by treatment group and time-to-event treatment differences will be analyzed using the log-rank test.

Duration of hospital stay excluding rehabilitation stay will be summarized by treatment group and analyzed using analysis of covariance with treatment and Baseline PVR in the model.

GFR will be summarized by treatment and time point (Baseline, Week 12/EOT) using descriptive statistics (n, mean, SD, median, Q1, Q3, and range). The change from Baseline to Week 12/EOT in GFR will be summarized similarly. Change from Baseline in GFR will be analyzed using an ANCOVA with a factor for treatment and covariates Baseline log PVR and Baseline GFR. The adjusted treatment effect and its 95% confidence interval will be presented.

11.3.5 Analysis of the safety variable(s)

The safety analyses described below 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 treatment. The number and percentage of patients experiencing treatment-emergent AEs and SAEs at least once will be tabulated by treatment group and by:

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

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

AEs leading to premature discontinuation of study treatment and 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 treatment, and for AEs leading to death.

11.3.5.2 Laboratory variables

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

The central laboratory manual outlines the definitions of marked abnormalities and provides guidance for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables are transformed to standard units. All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per-protocol) or unscheduled assessments.

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

Laboratory variables are the following:

- Hematology: hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential counts, platelet count
- Blood chemistry: AST, ALT, alkaline phosphatase, total and direct bilirubin, LDH, creatinine, BUN, uric acid, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, protein, albumin.

The number and percentage of patients with liver function test abnormalities [classified as in Section 11.2.4] will be tabulated by treatment group.

The number and percentage of patients with hemoglobin abnormalities [classified as in Section 11.2.4] will be tabulated by treatment group.

11.3.5.3 Vital signs and body weight

Blood pressure (i.e., DBP and SBP), pulse rate, and body weight (in kg) will be summarized at each study visit using the usual location and scale summary statistics by treatment group for both absolute values and changes from Baseline. Patients for whom no post-Baseline value is available are excluded from the analysis of the changes from Baseline in the SS.

11.4 Interim analyses

No interim analysis will be conducted.

An Independent Statistical Center will have access to the study data exclusively for review by the IDMC. The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter.

11.5 Sample size

11.5.1 Sample size justification

There are no randomized clinical trial data in this patient population. However, an integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), the hemodynamic substudy of SERAPHIN (AC-055-302), and the recently completed MERIT study (AC-055E201) of macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension, suggest that the treatment group difference on PVR is around −0.28 on log scale (ranged from −0.45 to −0.17 with 95% confidence interval: −0.35, −0.21) with the within group standard deviation (SD) around 0.40 on log scale (90% confidence interval:0.38, 0.42).

Based on the following assumptions:

- Type I error of 2.5% (1-sided);
- 80% power;
- Treatment assignment ratio 1:1 between placebo and macitentan 10 mg;
- Treatment group difference on PVR ratio of Week 12 to Baseline −0.28 (a GMR of 0.76 macitentan/placebo);
- Within group SD of 0.41;
- A normal distribution for the log-transformed percent of Baseline PVR;

70 evaluable patients will be needed for 80% power (35 patients per group) to test the primary hypothesis of interest. Accounting for 10% non-evaluable patients, approximately78 patients will need to be randomized.

11.5.2 Sample size sensitivity

Table 2 gives more details about the integrated analysis of PVR. It also shows the ‘best’ and ‘worst’ case sample sizes based on the 95% CLs around the treatment effect for each study as well as for the integrated analysis. It appears that the proposed sample size of 70 patients is robust to some deviations from the assumptions given above.

Table 2 Treatment effects (differences on log-scale as well as % reduction versus placebo), variability in integrated analysis of four studies (AC-052-366, AC-052-364, AC-055-302 and AC-055E201), and associated sample size for 80% power.

Study	Protocol	Treatment Effect		95% CI of Effect		SD	90% CI of SD		Sample Size[1]	Best Case	Worst Case
EARLY	AC-052-364	−0.26	−23%	−0.41	−0.11	0.50	0.45	0.54	120	50	652
BENEFIT	AC-052-366	−0.25	−22%	−0.35	−0.15	0.32	0.29	0.35	54	30	146
SERAPHIN	AC-055-302	−0.45	−36%	−0.58	−0.32	0.38	0.35	0.43	26	16	48
MERIT	AC-055E201	-0.17	−16%	−0.29	−0.01	0.39	0.35	0.45	166	58	> 1000
Overall		−0.28	−24%	−0.35	−0.21	0.40	0.38	0.42	66	44	114

[1]For 80% power and a two-sided alpha of 5%
Best case: based on lower limit of 95% CI for effect
Worst case: based on upper limit of 95% CI for effect
CI = confidence interval; PVR = pulmonary vascular resistance; SD = standard deviation.

12 DATA HANDLING

12.1 Data collection

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

eCRF data will be captured via electronic data capture. 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.

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE reports) submitted to Actelion and any external service providers, subjects must be identified only by number, and never by

name or initials, hospital numbers, or any other identifier. The investigator/delegate must keep a subject identification code list, at the site, showing the Screening/Randomization number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

Electronic CRFs will be used for all subjects. The investigator will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject 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 eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of Health Authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

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

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate SOP. After database closure, the investigator will receive the eCRFs of the subjects 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 subject (such as the Subject 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 or subject information leaflet after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

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

13.3 Informed Consent

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

The ICF will be provided in English.

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

The subject and/or legal representative must sign, personally date, and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated, and timed (if the first

study-mandated procedure was performed on the same day Informed Consent was obtained) by the authorized site staff listed on the Actelion DoA form.

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

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

13.4 Compensation to subjects and investigators

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

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

13.5 Protocol adherence/compliance

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

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

13.6 Protocol amendments

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

13.7 Essential documents and retention of documents

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

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

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

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

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

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

13.8 Monitoring

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

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

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

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

The PI must ensure that the eCRF is completed within 5 days after a subject's visit (site visit or phone call), and that all requested subject files (e.g., ICFs, medical notes/charts, and other documentation verifying the activities conducted for the study) are available for review by the monitor. The required site personnel must be available during monitoring visits and allow adequate time to meet with the monitor to discuss study related issues.

The investigator agrees to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized

or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

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

13.9 Investigator site file

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

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

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

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

If the PI changes, or if the site relocates, the monitor must be notified as soon as possible.

13.10 Audit

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

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

13.11 Inspections

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

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

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

13.12 Reporting of study results and publication

Study results will be documented in a clinical study report that will be signed by Actelion representatives.

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 the clinical study on Actelion's Clinical Trial Register and on external/national registries, as required by local law.

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

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

Authorship will be determined in accordance with the International Committee of Journal Editors 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

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15 APPENDICES

Appendix 1 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 2 Glossary

Term	Definition
Adverse Event (AE)	Any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment. AEs include: • Exacerbation of a pre-existing disease. • Increase in frequency or intensity of a pre-existing episodic disease or medical condition. • Disease or medical condition detected or diagnosed during the course of the study, even though it may have been present prior to the start of the study. • Continuous persistent disease or symptoms present at study start that worsen following the start of the study (i.e., signing of informed consent). • Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study. • Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment. A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.
Baseline	The last value obtained prior to first dose of study treatment.
Baseline Right Heart Catheterization (RHC)	The last hemodynamic measurements after LVAD implantation and prior to the first dose of study treatment.

Childbearing potential	A woman is considered to be of childbearing potential unless she meets at least one of the following criteria: • Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy. • Premature ovarian failure confirmed by a specialist. • Pre-pubescence, XY genotype, Turner syndrome, uterine agenesis. • Post-menopausal, defined as 12 consecutive months with no menses without an alternative medical cause (International Council for Harmonisation [ICH] M3 definition).
Hemoglobin recovery	Return of hemoglobin above the lower limit of the normal range or return to a value close to that at Baseline.
Hospitalization for heart failure (HF)	A hospitalization in which the principal diagnosis is HF.
Intensity of adverse events	Mild • The event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention. Moderate • The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed. Severe • The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.
Medical history	• Chronic medical conditions and new acute medical conditions within the past 6 months (e.g., anemia, hepatitis C infection, HIV infection, obstructive or restrictive lung disease, hypertension, renal disease) • Any previous life-threatening conditions, including date (e.g., myocardial infarction).
Moderate to severe restrictive lung disease (an exclusion criterion)	Total lung capacity < 60% of predicted value.

Post-menopausal	Twelve consecutive months with no menses without an alternative medical cause (ICH M3 definition).
Previous therapy	Any treatment for which the end date is prior to the signing of informed consent
Pulmonary Hypertension (PH)	• Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg *and* • Pulmonary artery wedge pressure (PAWP) ≤ 18 mmHg *and* • PVR > 3 Wood units.
Serious Adverse Event (SAE), as per ICH guidelines	Any AE fulfilling at least one of the following criteria • Fatal. • Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe. • Requiring inpatient hospitalization, or prolongation of existing hospitalization. • Resulting in persistent or significant disability or incapacity. • Congenital anomaly or birth defect. • Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.
Severe obstructive lung disease (an exclusion criterion)	Forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC) < 0.7 associated with FEV_1 < 50% of predicted value after bronchodilator administration.

Stabilization of the patient for 48 h prior to the Baseline RHC	• No LVAD pump speed/flow rate changes *and* • Stable dose of oral diuretics *and* • No intravenous (i.v.) inotropes or vasopressors *and* • Patient able to ambulate
Study-concomitant therapy	Any treatment for which the start date is on or after the signing of Informed Consent up to 30 days after study treatment discontinuation.
Study treatment	Administration of double-blind study drug (macitentan or placebo).
Study treatment-concomitant	Any treatment for which the start date is on or after the first administration of study treatment up to Week 12 or earlier in case of premature discontinuation of study treatment.