Macitentan / ACT-064992

Heart failure with preserved ejection fraction and pulmonary vascular disease

Protocol AC-055G202

SERENADE

A multi-center, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Macitentan / ACT-064992

Indication

Heart failure with preserved ejection fraction and pulmonary vascular disease

Protocol number, study acronym, study title

AC-055G202, SERENADE: A multi-center, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

I approve the design of this study.

Title	Name	Date	Signature
Clinical Trial Physician	William Byra	PPD	
Clinical Trial Scientist	Pranoti Pradhan		
Clinical Trial Statistician	Wentao Lu		

INVESTIGATOR SIGNATURE PAGE

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AC-055G202, SERENADE: A multi-center, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

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

I agree to conduct this study in accordance with the 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 independent ethics committee or institutional review board (IEC/IRB) 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 IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the subjects (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all subjects or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual subject. 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					

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6, Version 7	16-July-2020
Amendment 5, Version 6	06-February-2020
Amendment 4, Version 5	08-March-2019
Amendment 3, Version 4	10-April-2018
Amendment 2, Version 3	12-April-2017
Amendment 1, Version 2	08-February-2017
Original Protocol, Version 1	07-September-2016

Amendment 6 (16-Jul-2020)

Overall Rationale for the Amendment: The purpose of this amendment is to update the concomitant therapy sections pertaining to new information regarding a drug-drug-interaction of macitentan with moderate dual CYP3A4 and CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors.

Data from clinical trials with macitentan 10 mg were reviewed, identifying cases where macitentan 10 mg was administered concomitantly with dual CYP3A4 / CYP2C9 inhibitors, such as fluconazole and amiodarone. The review indicated that co-administration of fluconazole or amiodarone with macitentan was not common (between 1-3% of patients). No safety concerns were identified with concurrent administration of fluconazole or amiodarone and macitentan 10 mg.

A Protocol Amendment Summary of Changes Table for current amendment is provided below.

Section number and Name	Description of Change	Brief Rationale
5.2.5 Forbidden concomitant therapy	Further information on concomitant administration of CYP34A and CYP2C9 inhibitors was added. • Strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) **or moderate dual CYP3A4/CYP2C9 inhibitors (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine) until study intervention discontinuation**	To add moderate dual CYP3A4/CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4- and moderate CYP2C9 inhibitors to the list of forbidden medications.
	• **If subjects are currently stable on a moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g. miconazole, piperine), the subject may remain on current treatment per the investigator's discretion, based on his/her clinical judgement and risk-benefit assessment.**	As we are adding on a new group of forbidden therapy during the study, it will not necessarily apply to subjects who are already well managed on such an ongoing combination.
5.2.5 Forbidden concomitant therapy; 13 References	A new reference was added to Section 5.2.5 and updated in the reference list.	To provide investigators with examples of CYP3A4 and CYP2C9 inhibitors

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BCRP	Breast-cancer resistant protein
BMI	Body mass index
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical Event Committee
CFR	Code of Federal Regulations (US)
CHF	Chronic heart failure
CI	Confidence interval
CL	Confidence limit
CO	Cardiac Output
COPD	Chronic obstructive pulmonary disease
CpcPH	Combined post- and pre-capillary pulmonary hypertension
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed tomography
CTA	Computed tomography angiography
CTT	Clinical Trial Team
CV	Cardiovascular

CYP3A4	Cytochrome P-450 3A4
DAOH	Days alive and out of the hospital
DBP	Diastolic blood pressure
DPG	Diastolic Pulmonary Vascular Pressure Gradient
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1
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
GFR	Glomerular Filtration Rate
GQM	Global Quality Management
HDL	High-density lipoprotein
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate
i.v.	Intravenous
IB	Investigator's Brochure
ICD	Implantable cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrial
LAV	Left atrial volume
LAVI	Left atrial volume index
LDL	Low-density lipoprotein
LV	Left ventricular
LVD	Left ventricular dysfunction
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NSTEMI	Non-ST-segment elevation myocardial infarction
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label enrollment
PAD	Peripheral artery disease
PAH	Pulmonary arterial hypertension
PASP	Pulmonary artery systolic pressure
PAWP	Pulmonary artery wedge pressure
PCI	Percutaneous coronary intervention
PDE-5	Phosphodiesterase-5
PE	Pulmonary embolism
PGA	Patient’s global assessment
PH	Pulmonary hypertension
PI	Principal Investigator
PPS	Per-protocol Analysis Set

PTOP	Post-treatment observation period
PVD	Pulmonary vascular disease
PVR	Pulmonary vascular resistance
QS	Quality System
RA	Right atrial
RAAS	Renin-angiotensin-aldosterone system
RHC	Right heart catheterization
RSI	Reference safety information
RV	Right ventricular
RVD	Right ventricular dysfunction
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SIV	Site initiation visit
SpO_2	Oxygen saturation
STEMI	ST-segment elevation myocardial infarction
SUSAR	Suspected unexpected serious adverse reaction
TAPSE	Tricuspid annular plane systolic excursion
TIA	Transient ischemic attack
TLC	Total lung capacity
TR	Tricuspid regurgitation
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
V/Q	Ventilation/perfusion
VLDL	Very low-density lipoprotein
WHF	Worsening heart failure
WHO	World Health Organization

PROTOCOL SYNOPSIS AC-055G202

TITLE	A multi-center, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease
ACRONYM	SERENADE Macitentan in heart failure with pre**SER**ved ej**E**ction fractio**N** and pulmon**A**ry vascular **D**iseas**E**
OBJECTIVES	**Primary objective** To evaluate whether macitentan 10 mg reduces n-terminal pro-brain natriuretic peptide (NT-pro-BNP) versus placebo at Week 24 in subjects with heart failure with preserved ejection fraction (HFpEF) and pulmonary vascular disease. **Secondary objectives** To evaluate the effect of macitentan 10 mg as compared to placebo on: • Quality of life • Daily physical activity • Worsening of heart failure **Other objectives** Other objectives are described in Section 2.3.
DESIGN	A prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group design Phase 2b study. Subjects will be randomized in a 1:1 ratio to either macitentan or placebo. Treatment allocation will be stratified by NT-proBNP level (< 1000 pg/mL and ≥ 1000 pg/mL) at macitentan run-in entry.
PERIODS	**Screening period:** Lasts up to 30 days; starts with the signature of the Informed Consent Form at Visit 1 and ends prior to administration of the first dose of study treatment at Visit 2. **Run-in period:** 9-week run-in period consisting of a single-blind placebo run-in of 4 weeks, followed by a single-blind macitentan run-in of 5 weeks.

	The placebo run-in starts with administration of the first dose of placebo at Visit 2 and ends on the day before Visit 4. The macitentan run-in starts with the administration of the first dose of macitentan at Visit 4 and ends with the subject's randomization at Visit 6. **Double-blind treatment period:** The double-blind treatment period consists of 2 phases: *Core phase:* The double-blind core phase will last for 24 weeks. It starts with the administration of the first dose of double-blind study treatment and ends on the day before Visit 11 (Week 24). Subjects who are still in the core phase at the time of global protocol Version 6 approval will end treatment at 24 weeks and will not proceed to the extension phase [see Section 3.1.1.8]. *Extension phase:* The double-blind extension phase will last for 28 weeks. It starts on the day of Visit 11 (Week 24) and ends on the day of last study treatment intake. Subjects who are in the extension phase at the global protocol Version 6 approval will return for an EOT visit within 60 days, but no later than Week 52. **Post-treatment observation period:** Subjects who prematurely discontinue double-blind study treatment (core or extension phase) will be asked to enter a post-treatment observation period (PTOP), which ends 52 weeks after randomization. The PTOP starts with visit PTOP1, which corresponds to the safety follow-up visit. Thereafter, visits are scheduled at Week 24 (PTOP2), Week 36 (PTOP3) and Week 52 (PTOP4), depending on time point of premature discontinuation. Subjects who have not completed Week 24 at the time of global protocol Version 6 approval, will end PTOP at 24 weeks (PTOP2) [see Section 3.1.1.8]. **Safety follow-up period:** The safety follow-up period starts on the day after the last dose of study treatment and ends 30 days thereafter with the End-of-Study (EOS) visit, or PTOP1 visit for those subjects who prematurely discontinue study treatment.

	End-of-Study: EOS is reached when the safety follow-up period or, if applicable, PTOP have been completed. For an individual subject, the study is completed with the EOS visit, which is either Visit 14 (safety follow-up visit) for subjects who completed the treatment period as per protocol, or PTOP4 for subjects who prematurely discontinued. **Transition to the SERENADE OL extension study (AC-055G203):** Subjects who remain in the SERENADE study for 52 weeks after randomization may transition to the SERENADE OL (AC-055G203) study if they meet the eligibility criteria defined in the SERENADE OL protocol. Eligible subjects who are consented to global protocol Version 6 will be allowed to transition to the SERENADE OL study if they remained in the SERENADE study for 24 weeks after randomization [see Section 3.1.1.8].
PLANNED DURATION	Approximately 2.5 years from first subject, first visit to last subject, last visit.
SITE(S) / COUNTRY(IES)	77 sites in 17 countries.
SUBJECTS / GROUPS	It was planned to enroll 300 subjects in 2 groups; randomized in a 1:1 ratio (150 subjects per group) by an interactive Voice/Web System to macitentan or placebo using the NT-proBNP value observed before entry in macitentan run-in as a stratification factor. Following closure of Screening on 27 December 2019, it is expected that approximately 140 subjects will be randomized.
INCLUSION CRITERIA	1. Signed informed consent prior to any study-mandated procedure 2. Male or female subjects ≥ 18 years of age 3. Signs or symptoms of heart failure (HF) requiring treatment with at least one oral diuretic (any type) 4. Left ventricular ejection fraction (LVEF) ≥ 40% (by echocardiography at Screening) 5. New York Heart Association (NYHA) functional class (FC) II to III

	6. Criterion removed (see footnote[1]) 7. Patients with HFpEF defined as either one of the following by echocardiography at Screening: a. Left atrial (LA) enlargement: i. Left atrial volume > 58 mL (male) / > 52 mL (female) *or* ii. Left atrial volume index ≥ 28 mL/m^2, *or* iii. LA area > 20 cm^2, *or* iv. LA diameter > 4.0 cm (male) / > 3.8 cm (female) b. Left ventricular septal thickness or posterior wall thickness ≥ 1.1 cm 8. Elevated NT-proBNP / BNP ≥ 200 / 60 pg/mL for subjects in sinus rhythm or ≥ 500 / 150 pg/mL for subjects with atrial fibrillation (AF) at any time within 3 months prior to Screening or at Screening 9. Pulmonary vascular disease or right ventricular (RV) dysfunction meeting <u>at least one</u> of the following for echocardiographic (at Screening) and/or right heart catheterization (RHC) parameters (at Screening or from any RHC previously performed): a. Echocardiographic peak TR velocity > 2.8 m/s *or* invasive mean pulmonary artery pressure ≥ 25 mmHg (RHC) *or* PASP > 40 mmHg **and** evidence of RV dysfunction (TAPSE < 17 mm *or* RV fractional area change < 35% *or* RV tissue Doppler s' velocity < 9.5 cm/s) b. Diastolic Pulmonary Vascular Pressure Gradient (DPG) > 5 mmHg (RHC) c. Pulmonary vascular resistance (PVR) > 3 Wood Units (RHC) 10. A woman of childbearing potential must have a negative pre-treatment serum pregnancy test, agree to use reliable contraception from at least 30 days prior to Visit 2 up to at least 30 days after study treatment discontinuation, and

[1] Inclusion criterion 6 (HF hospitalization within 12 months prior to Screening or RHC within 6 months prior to Screening showing PAWP/LVEDP > 15mmHg) was removed in Global Protocol v.4.

	agree to undertake monthly pregnancy tests from Screening up to at least 30 days after study treatment discontinuation.
EXCLUSION CRITERIA	**Disease-related** 1. Any prior valid measurement of LVEF < 40% **Cardiovascular comorbidities:** 2. Significant unrepaired structural valvular heart disease (i.e., greater than mild aortic or mitral stenosis, and greater than moderate aortic or mitral regurgitation) 3. Hypertrophic, restrictive, and infiltrative cardiomyopathies 4. Pericardial disease 5. Acute coronary syndrome, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable coronary artery disease or has undergone coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) within 3 months of screening. 6. Known indication for PCI or CABG 7. Uncontrolled heart rate (HR) from atrial fibrillation or atrial flutter (> 110 beats per minute) as assessed by ECG 8. History of serious life-threatening or hemodynamically significant arrhythmias, including symptomatic or sustained ventricular tachycardia or defibrillator shock within 12 month(s) of Screening 9. History of or anticipated heart transplant or anticipated/implanted ventricular assist device 10. Transient ischemic attack (TIA) or stroke within 3 months of Screening 11. Systolic blood pressure (SBP) ≥ 180 mmHg or diastolic blood pressure (DBP) ≥ 110 mmHg **Other causes of right heart failure not associated with left ventricular dysfunction:** 12. Significant parenchymal lung disease fulfilling any of the following:

	a. Forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC ratio) < 0.7 associated with FEV_1 < 50% of predicted value after bronchodilator administration in subjects with a known or suspected history of significant lung disease. b. Known moderate or severe restrictive lung disease, e.g., total lung capacity (TLC) < 60% (predicted) c. Clinical suspicion of diffuse interstitial fibrosis or alveolitis, unless excluded by high resolution computed tomography (CT) d. Clinical suspicion of pulmonary thromboembolism within 12 months prior to Screening, unless excluded by ventilation/perfusion (V/Q) scan or computed tomography angiography (CTA) 13. Criterion removed (see footnote[2]) 14. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF. **Criteria related to macitentan use:** 15. Administration of pulmonary arterial hypertension-specific therapy (i.e., endothelin receptor antagonists, prostanoids, phosphodiesterase-5 [PDE-5] inhibitors, guanylate cyclase stimulators) within 1 month prior to Screening 16. Hypotension, i.e., SBP < 90 mmHg or DBP < 50 mmHg 17. Severe renal dysfunction with an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula 18. Known and documented severe hepatic impairment, e.g., Child-Pugh Class C

[2] Exclusion criterion 13 (BMI ≥ 45 kg/m^2) was removed in Global protocol v.4.

	19. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 3 × the upper limit of normal at Screening 20. Hemoglobin < 100 g/L (< 10 g/dl) at Screening 21. Plan to become pregnant or lactating 22. Treatment with strong cytochrome P-450 3A4 (CYP3A4) inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, or St. John's wort within 1 month prior to Screening Treatment with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir within 1 month prior to Screening 23. Criterion removed (see footnote[3]) 24. Known hypersensitivity to macitentan or drugs of the same class, or any of the excipients (e.g., soy lecithin, lactose) **General criteria:** 25. Planned or current treatment with another investigational treatment within 2 months prior to screening 26. Inadequate control of comorbidities according to current standards of care, as per judgment of the investigator 27. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease 28. Known concomitant life-threatening disease with a life expectancy < 12 months.

[3] Exclusion criterion 24 (treatment with BCRP substrates) was removed in Global protocol v.4.

RUN-IN FAILURE CRITERIA	A subject must be discontinued from the study in case any of the following criteria is fulfilled at any time during the run-in period: 1. Study treatment compliance < 80% 2. Central laboratory results showing a decrease in hemoglobin by > 50 g/L from Screening or hemoglobin < 80 g/L or need for transfusion 3. Significant fluid retention / worsening of HF as evidenced by one of the following: a. Administration of i.v. diuretics due to fluid retention b. Addition of high potency thiazide diuretic (metolazone, indapamide), ≥ 100% increase in loop diuretic to a total oral dose ≥ 120 mg of furosemide equivalents/day [see Section 4.5]. c. Increase in body weight by ≥ 5% or ≥ 5 kg from the value at the start of the corresponding run-in period (i.e., Visit 2 and Visit 4 for the placebo and macitentan run-in, respectively) due to fluid overload d. Worsening in NYHA FC e. Hospitalization for worsening of HF 4. Any adverse events (AEs) that preclude continuation based on the investigator's judgment.
STUDY TREATMENTS	**Investigational treatment** Macitentan oral tablet, 10 mg once daily. **Comparator** Matching placebo, once daily.
AUXILIARY MEDICINAL PRODUCTS	All subjects must be on oral diuretic therapy (any type).
ENDPOINTS	**Primary efficacy endpoint** • Percent of baseline NT-proBNP assessed at Week 24 **Secondary efficacy endpoints** • Change from baseline to Week 24 in the clinical summary score (as assessed by the Kansas City Cardiomyopathy Questionnaire [KCCQ]) • Change from baseline to Week 24 in accelerometer-assessed proportion of time spent in light to vigorous

	physical activity based on a threshold of > 100 activity counts per minute • Time to worsening heart failure (WHF) event over 52 weeks. • **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Safety endpoints** • All-cause death up to 30 days after study treatment discontinuation • Number of all-cause hospital admissions up to 30 days after study treatment discontinuation • Treatment-emergent AEs and serious adverse events (SAEs) up to 30 days after study treatment discontinuation • AEs leading to premature discontinuation of study treatment • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight up to 30 days after study treatment discontinuation • Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation • Change from baseline in eGFR up to 30 days after study treatment discontinuation • Decrease from baseline in SBP of ≥ 5% and SBP < 100 mmHg up to 30 days after study treatment discontinuation.
ASSESSMENTS	Refer to the schedule of assessments in Table 1, Table 2, Table 3, and Table 4.
STATISTICAL METHODOLOGY	**Analysis sets** The Screened Analysis Set includes all subjects who are screened and have a subject identification number. The placebo run-in Set includes all screened subjects who enter the placebo run-in and receive at least one dose of study treatment in single-blind placebo run-in. The macitentan run-in Set includes all subjects who have completed the placebo run-in, enter the macitentan run-in and

	receive at least one dose of study treatment in single-blind macitentan run-in. The Full Analysis Set (FAS) includes all subjects randomized to double-blind study treatment. The Per-protocol Analysis Set comprises all randomized subjects who received double-blind study treatment and who complied with the protocol sufficiently to allow a reliable assessment of the treatment effect on the primary efficacy endpoint. The Safety Set includes all subjects who received at least one dose of double-blind study treatment. **Primary efficacy variable** The primary efficacy variable is the percent of baseline in NT-proBNP at Week 24. For subjects without available NT-proBNP value at Week 24, the last available value observed before Week 24 will be carried forward and considered for the main analysis. Percent of baseline is calculated as the ratio of the Week 24 NT-proBNP value over baseline value, expressed in percentage. **Null and alternative hypotheses** Due to the underlying log-normal distribution of the primary efficacy variable, an analysis of covariance (ANCOVA) will be applied on log-transformed data. The null hypothesis is that macitentan and placebo effects on NT-proBNP are the same. The alternative hypothesis is that the effect of macitentan on NT-proBNP differs from placebo effect. The null hypothesis will be tested by a 2-sided Wald test with a 2-sided significance level of 0.10. **Primary statistical analysis** The main analysis will be performed on subjects of the FAS, according to the intent-to-treat principle. The main analysis of the primary efficacy variable will be carried out after log-transformation using ANCOVA, adjusting

	for the log of the ratio: baseline NT-proBNP over NT-proBNP value as per Interactive Response Technology system [IRT] with an overall type I error of 10% 2-sided. The treatment effect expressed as geometric means ratio and its associated 90% 2-sided confidence interval (CI) will be estimated based on the same model by inversely transforming, using the exponential function, the Least Squares Mean and 90% CI obtained in log scale. **Key secondary efficacy variables** The three key secondary efficacy variables will be tested using a hierarchical testing approach to address multiplicity concern. The change from baseline to Week 24 in KCCQ clinical summary score and accelerometer-assessed physical activity will be analyzed by means of an ANCOVA adjusting for the variable baseline value and for the log of the ratio: baseline NT-proBNP over NT-proBNP value as per IRT. Least Squares Estimates within each treatment group and between treatment groups will be displayed along with 90% 2-sided CIs and p-values. The analysis of time to first occurrence of WHF event will be explored using a proportional hazards Cox model adjusting for the log of the ratio: baseline NT-proBNP over NT-proBNP value as per IRT. Estimate of HR and its associated 90% CI and p-value will be displayed. Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at relevant time points for each treatment group and displayed in both a graphical and a tabular form. **Safety variables** The number and percentage of: • All-cause deaths occurring up to 30 days after study treatment discontinuation • Subjects with at least one treatment-emergent AE occurring up to 30 days after study treatment discontinuation • Subjects with at least one SAE occurring up to 30 days after study treatment discontinuation • Subjects with at least one AE leading to premature discontinuation of study treatment

	will be tabulated by treatment group and by System Organ Class and Preferred Term. The number of recurrent all-cause hospital admissions will be estimated using a Negative binomial regression model. Marked laboratory abnormalities will be summarized for each laboratory variable by treatment group providing their incidence and frequency. For selected laboratory variables (erythrocytes, hemoglobin, hematocrit, AST, ALT, total bilirubin and alkaline phosphatase), absolute values and changes from baseline will be summarized over time up to 30 days after study treatment discontinuation. Vital signs, body weight and GFR will be described over time up to 30 days after study treatment discontinuation by means of random coefficient regression models. Decreases in SBP will be summarized by treatment group providing the number and percentage of subjects with, for at least one post-baseline assessment and up to 30 days after study treatment discontinuation, a percent change from baseline $\leq -5\%$ and an SBP < 100 mmHg at the time of assessment. **Sample size** A number of 300 randomized subjects is adequate to detect a geometric means ratio of 0.75 (macitentan over placebo, -0.288 in log scale) corresponding to a 25% improvement with a power of 80% and a type I error of 0.10 2-sided, when considering a standard deviation of 1 in log scale and using the Wald test. The critical value expressed as geometric means ratio is 0.83. Following closure of Screening on 27 December 2019, it is expected that approximately 140 subjects will be randomized. With the same assumptions as above for the reduced sample size of 140, the critical value expressed as geometric means ratio is 0.76.
STUDY COMMITTEES	An Independent Data Monitoring Committee (IDMC) has overall responsibility for safeguarding the interests of subjects by monitoring benefit-risk ratio and making appropriate recommendations based on all the reported data and 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. Both a Scientific Advisory Board and a Steering Committee are involved in the study design and will be consulted prior to and during the study for relevant medical issues and study publications. An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) has been appointed to provide ongoing assessment and advice regarding serious hepatic AEs of special interest that require further evaluation during the study as per the ILSDRB charter.

PROTOCOL

1 BACKGROUND

Endothelin-1 (ET-1), a 21 amino acid peptide, is one of the most potent vasoconstrictors, and plays a key role in vascular tone and pathophysiology of cardiovascular disease [Inoue 1989, Levin 1996, Galiè 2004]. The two ET-1 receptors, ET_A and ET_B, 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 on endothelial, epithelial, endocrine and nerve 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].

The endothelin system has been shown to be activated in chronic heart failure (CHF), among other neurohumoral systems, such as the sympathetic and RAAS [Jessup 2003]. Plasma big ET-1 and ET-1 levels were found to be elevated and inversely correlated with clinical and hemodynamic measures of prognosis in patients with CHF, including patients with stable CHF [Kiowski 1995, Pacher 1996, Wei 1994, Parker 2004, Hulsmann 1998]. Big ET-1 and C-terminal pro-ET-1 have been shown to independently predict mortality and morbidity in CHF [Masson 2006, Jankowska 2011].

In nonclinical studies in animal models of experimental heart failure (HF) treatment with dual or ET_A selective antagonists significantly improved left ventricular dysfunction, prevented ventricular remodeling and prolonged survival [Cowburn 2001, Wada 1997].

Several endothelin receptor antagonist (ERAs) have been shown to improve pulmonary hemodynamics, exercise capacity, functional status, and clinical outcome in pulmonary arterial hypertension (PAH) and are approved for PAH treatment [Galiè 2015]; however, ERAs tested in acute and chronic HF have not consistently shown clinical benefit and new studies are warranted [Kaoukis 2013].

1.1 Indication

HF is a common, disabling and potentially fatal condition, which is the leading cause of hospitalization in persons over 65 years of age. HF is a major public health issue, with an estimated prevalence of over 5.8 million in the USA, and over 23 million worldwide [Bui 2011, McMurray 1998]. Approximately 1% to 2% of the adult population in the developed countries has HF, and rising to ≥ 10% among persons of 70 years of age or older [McMurray 2012, Mosterd 2007].

In the USA, projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age with HF. It is estimated that 870,000 new cases of HF are diagnosed every year in the USA. The incidence of HF is nearly 10 per 1000 population over 65 years of age. Nearly 300,000 deaths occur annually that are directly attributable to HF [Mozaffarian 2015].

The estimated prevalence of heart failure with preserved ejection fraction (HFpEF) among all HF patients ranges from 40% to 71% in different studies [Bishu 2013, Oktay 2013, Bui 2011, Brouwers 2013, Tiller 2013]. With increasing prevalence in recent years, HFpEF may become the predominant form of HF in the coming decades [Oktay 2013]. HFpEF has been variably classified as ejection fraction > 40%, > 45%, > 50%, and ≥ 55%. The criteria proposed to define the syndrome of HFpEF include a) clinical signs or symptoms of HF; b) evidence of preserved or normal left ventricular ejection fraction (LVEF); and c) evidence of abnormal left ventricular (LV) diastolic dysfunction (the filling of the left heart) that can be determined by Doppler echocardiography or cardiac catheterization [Vasan 2000]. HFpEF seems to have a different epidemiological and etiological profile from heart failure with reduced ejection fraction (HFrEF) [McMurray 2012]. Patients with HFpEF are predominantly elderly, more likely to be female than male, and have a high prevalence of comorbidities such as hypertension, coronary artery disease (CAD), diabetes mellitus, obesity, anemia, chronic kidney disease, atrial fibrillation, and chronic obstructive pulmonary disease [Bishu 2013, Oktay 2013, Bui 2011, Borlaug 2014].

Dysfunction of the right ventricular-pulmonary vascular unit is a common entity in HFpEF and is recognized to confer poor outcomes in these patients, including increased HF hospitalization and higher overall cardiovascular mortality. Right ventricular dysfunction (RVD) develops in response to elevated afterload and pulmonary vascular dysfunction, and is evolving to be a significant modifier of both natural history and prognosis in patients with HFpEF. The prognostic significance of RVD in HFpEF has been shown to be independent of, and additive to, the severity of pulmonary hypertension (PH) [Zakeri 2015b] and was the strongest predictor, more predictive than severity of PH, of death in 96 HFpEF patients [Melenovsky 2014].

1.2 Study treatment(s)

Macitentan (ACT-064992, Opsumit®) is an orally active, non-peptide, potent dual endothelin ET_A and ET_B ERA which has been approved for the treatment of PAH. ERAs are being developed for a variety of diseases associated with the deleterious effects of ET, particularly in the pulmonary and cardiovascular fields.

For detailed information on macitentan, please see the most recent version of the macitentan Investigator's Brochure (IB) [Macitentan IB].

For detailed information on 'Special warnings and precautions' and 'General precautions', please see sections 1.7 and 1.8 of the most recent version of the macitentan IB [Macitentan IB].

1.3 Purpose and rationale of the study

Current HF therapy is largely based on digitalis and diuretics associated with various combinations of renin-angiotensin-aldosterone system (RAAS)- and beta blockers. In contrast to HFrEF, there is no approved therapy for HFpEF patients despite several attempts to mitigate the diastolic dysfunction through blockade of the RAAS, beta blockade and phosphodiesterase-5 (PDE-5) inhibitors [Yancy 2013, Shah 2013, Pfeffer 2015]. Today, HFpEF patients, particularly those with associated PH, are empirically treated for their underlying condition (e.g., hypertension, diabetes) and with diuretics for fluid retention.

The HFpEF population presents a high prevalence of comorbidities that are associated with increased ET-1 production, e.g., sleep apnea, metabolic syndrome, diabetes, obesity and age. Nonclinical studies demonstrated that ERAs were effective in preventing or attenuating the cardiovascular complications (hypertension, endothelial dysfunction, renal failure, cardiac remodeling) of these risk factors [Mulder 1976, Maczewski 2000, Belaidi 2009, Iglarz 2008]. Cardiac remodeling can be attributed in part to ET-1, based on its known profibrotic and hypertrophic properties [Schwarz 2002]. Recent preliminary data demonstrated efficacy of ET receptor blockade with macitentan on LV remodeling without significantly affecting systemic blood pressure (BP) [Richard V, et al. Actelion data on file; Sam 2015]. Taken together, these data suggest that dual ET receptor blockade can directly improve LV remodeling, and especially decrease fibrosis, leading to an improvement of the filling capacity of the left ventricle.

Most studies with ERAs did not demonstrate clinical benefit in chronic HF; treatment with ERAs has been associated with fluid retention, which may worsen HF symptoms [B-166849, B-02.005, D-05.036, Lüscher 2002, Anand 2004, Abraham 2001]. Treatment with ERAs has been also associated with increased incidence of edema in PAH patients [Aversa 2015]. However, in patients with HFpEF, treatment with sitaxentan for 6 months significantly increased exercise tolerance as measured by treadmill time. There was no significant difference in the overall occurrence of adverse events (AEs) between sitaxentan and placebo, while peripheral edema was reported for 19.7% and 15.6% in the sitaxentan and placebo groups, respectively, over 6 months of treatment [Zile 2014].

In a Phase 2 exploratory study in 63 subjects with combined post- and pre-capillary pulmonary hypertension (CpcPH), AC-055G201/MELODY-1 [Vachiéry 2018], the main composite safety endpoint, i.e., the proportion of subjects experiencing either significant fluid retention (defined as an increase in body weight due to fluid overload by≥ 5kg or ≥ 5%, or intravenous (i.v.) administration of diuretics) or a worsening in New York Heart

Association (NYHA) functional class (FC) up to End-of-Treatment (EOT), was more frequently met in the macitentan group: 7 subjects on macitentan (23%) compared to 4 subjects on placebo (13%). Occurrence of edema was observed early in the course of this trial in patients treated with macitentan and was generally well managed by diuretic enhancement. The occurrence of a fluid retention event was more frequent in the macitentan group (6.4%) compared to the placebo group (1.6%) during the first 4 weeks from the start of study treatment, while it was similar in both treatment groups beyond 4 weeks of study treatment (5.1% on macitentan versus 4.8% on placebo). This observation suggests that the susceptibility to fluid retention manifested early and stabilized over time.

A higher number of subjects on macitentan experienced at least one serious adverse event (SAE) (11 subjects [35%] on macitentan; 6 subjects [18.8%] on placebo), discontinued study treatment prematurely (7 subjects [22.6%] on macitentan; 4 subjects [12.5%] on placebo), or were hospitalized for worsening of HF (5 subjects [16.1%] on macitentan; 2 subjects [6.3%] on placebo). This difference was driven by the subjects who met the main safety point.

Although the MELODY-1 study was not powered to assess the efficacy of macitentan, the improvements observed in cardiac output (CO) (Hodges-Lehmann's median treatment difference of 0.6 L/min, 95% confidence limit [CL] 0.20, 1.10 at Week 12) and n-terminal pro-brain natriuretic peptide (NT-pro-BNP) (23% reduction compared to placebo at Week 12) may indicate a potential benefit with macitentan in the explored indication. The results of the study also showed that the hemodynamic characteristics of subjects with CpcPH included in the MELODY-1 study are similar to those with HFpEF and pulmonary vascular disease, therefore macitentan may present a potential benefit for subjects with HF, specifically HFpEF and pulmonary vascular disease with or without overt RVD whereby the increased right ventricular afterload could be mitigated by ERA treatment.

The purpose of this present study is to confirm the MELODY-1 findings on NT-proBNP and evaluate whether favorable findings from this earlier study translate into a clinically meaningful benefit in a subset of HFpEF patients with pulmonary vascular disease and who tolerate macitentan lending support for the further development in this indication.

1.4 Summary of known and potential risks and benefits

The results of the MELODY-1 study have shown that treatment with macitentan reduces NT-proBNP, a marker reflecting cardiac load and LV wall stress, and improves CO. These findings suggest that macitentan may have a beneficial effect in subjects with HFpEF and pulmonary vascular disease. However, the MELODY-1 results also showed an increased incidence of fluid retention events which led to worsening of HF in the macitentan group [Section 1.3]. The timing of these events suggests that fluid retention under macitentan therapy manifests early and stabilizes over time. To mitigate adverse effects caused by fluid retention, the study contains a placebo run-in phase to ensure that subjects are stable

and on optimal background therapy, and a macitentan run-in during which subjects are closely monitored and discontinued from the study if pre-defined criteria indicative of poor tolerability are met [see Section 4.5].

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.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to evaluate whether macitentan 10 mg reduces NT-pro-BNP versus placebo at Week 24 in subjects with HFpEF and pulmonary vascular disease.

2.2 Secondary objectives

The secondary objective of the study is to evaluate the effect of macitentan 10 mg as compared to placebo on:

- Quality of life
- Daily physical activity
- Worsening of heart failure.

2.3 Other objectives

- To evaluate the effects of macitentan 10 mg as compared to placebo on:
  - Cardiovascular deaths and hospitalizations
  - NYHA FC
  - Clinical composite outcome measure
  - Echocardiographic measures of cardiac function and structure.

2.4 Safety objective

To evaluate the safety and tolerability of macitentan 10 mg in subjects with HFpEF and pulmonary vascular disease.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group Phase 2b study [Figure 1].

It was planned that approximately 300 subjects would be randomized in a 1:1 ratio to either macitentan or placebo. Treatment allocation will be stratified by NT-proBNP level at macitentan run-in entry. The study is being conducted in 77 sites in 17 countries.

Following closure of Screening on 27 December 2019, it is expected that approximately 140 subjects will be randomized [see Section 3.1.1.8].

3.1.1 Study periods

The study comprises the following consecutive periods.

3.1.1.1 Screening period

Lasts up to 30 days; starts with the signature of the Informed Consent Form (ICF) at Visit 1 and ends prior to administration of the first dose of study treatment at Visit 2.

3.1.1.2 Run-in period

The run-in period consists of 2 parts: a placebo run-in and a macitentan run-in.

The run-in period starts with a single-blind placebo run-in of 4 weeks which starts with administration of the first dose of placebo at Visit 2 and ends on the day before Visit 4 (macitentan run-in start).

The placebo run-in is followed by a single-blind macitentan run-in of 5 weeks, which starts with administration of the first dose of macitentan at Visit 4 and ends with the subject's randomization at Visit 6.

3.1.1.3 Treatment period

The double-blind treatment period consists of 2 phases:

Core phase: The double-blind core phase will last for 24 weeks. It starts with the administration of the first dose of double-blind study treatment and ends on the day before Visit 11 (Week 24). The main aim of the core phase is to determine the 24-week effect of macitentan on the primary efficacy endpoint, NT-proBNP**.**

Subjects who are in core phase at the time of global protocol version 6 approval, will end treatment at 24 weeks and will not proceed to the extension phase of the study [see Section 3.1.1.8].

Extension phase: The double-blind extension phase will last for 28 weeks. It starts on the day of Visit 11 (Week 24) and ends on the day of last study treatment intake. The main aim of the extension phase is to collect further morbidity and mortality data.

Subjects who are in the extension phase at the global protocol Version 6 approval will return for an EOT visit within 2 months, but no later than Week 52.

3.1.1.4 Post-treatment observation period

Subjects who prematurely discontinue double-blind study treatment (core or extension phase) will be asked to enter a post-treatment observation period (PTOP), which ends 52 weeks after randomization. The PTOP starts with visit PTOP1, which corresponds to the safety follow-up visit. Thereafter, visits are scheduled at Week 24 (PTOP2), Week 36 (PTOP3) and Week 52 (PTOP4), depending on time point of premature discontinuation. If the safety follow-up visit (PTOP1) falls within the time-window of any of the other PTOP visits, then the corresponding PTOP visit and the safety follow-up visit can be combined. The assessments that are performed at each visit are described in the visit and assessment schedule [Table 4] for subjects entering the PTOP. Subjects who have not completed Week 24 at the time of global protocol Version 6 approval, will end the PTOP at Week 24 (PTOP2). Subjects who are past Week 24 at the time of consenting to global protocol Version 6 will return for an EOT visit within 2 months but no later than Week 52 and will then proceed to enroll in the OL study, if eligible, or complete EOS, if not eligible to enter SERENADE OL [see Section 3.1.1.8].

3.1.1.5 Safety follow-up period

The safety follow-up period starts on the day after the last dose of study treatment and ends 30 days thereafter with the End-of-Study (EOS) visit, or PTOP1 visit for those subjects who prematurely discontinue study treatment.

The visit schedule and protocol-mandated procedures will be performed according to the table of assessments [Table 2, Table 3, and Table 4] and are described in Section 7.

3.1.1.6 End-of-Study

EOS is reached when the safety follow-up period or, if applicable, PTOP have been completed. For an individual subject, the study is completed with the EOS visit, which is either Visit 14 (safety follow-up visit) for subjects who completed the treatment period as per protocol, or PTOP4 for subjects who prematurely discontinued study treatment.

3.1.1.7 SERENADE OL extension (study AC-055G203)

Subjects who remained in SERENADE (main study) for 52 weeks after randomization may be eligible for transition to the SERENADE OL study. Subjects who consented to global protocol Version 6, are eligible to transition to SERENADE OL if they remained in the main study for at least 24 weeks [see Section 3.1.1.8].

3.1.1.8 Change in duration of double-blind treatment period per Global protocol Version 6

Applicable to subjects who consented to global protocol version 6.

With global protocol Version 6, subjects will stop study treatment at Week 24 (Visit 11) and may be eligible to transition to SERENADE OL at this timepoint. Subjects who have passed Week 24 at the time of consenting to global protocol Version 6 will be scheduled to come back for an EOT visit within 2 months but no later than Week 52 and will then proceed to enroll in the OL study, if eligible, or complete EOS, if not eligible to enter SERENADE OL.

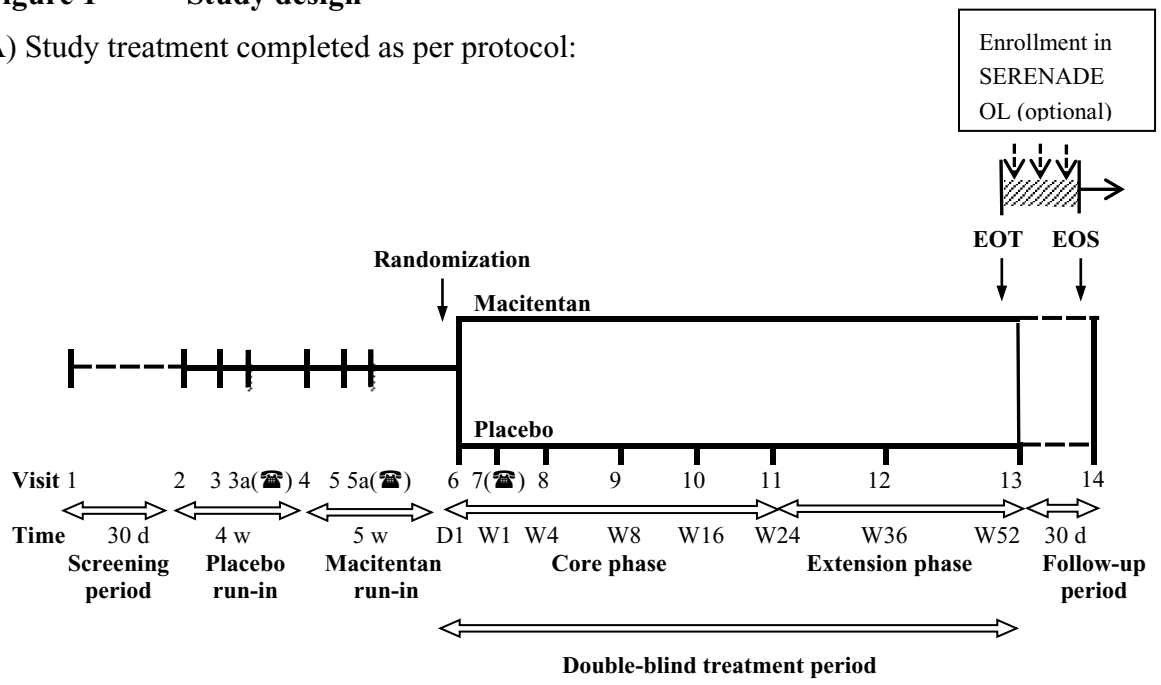
The reason for treatment discontinuation to be recorded in the eCRF for these subjects will be 'sponsor decision', unless an additional reason led to discontinuation of study treatment (e.g., AE).

Subjects who prematurely discontinue study treatment will remain in PTOP up to Week 24 (PTOP 2) and may transition to SERENADE OL if the eligibility criteria are met. Subjects who are past PTOP2 at the time of consenting to global protocol Version 6 will return for an EOS visit within 60 days but no later than Week 52 and may transition to SERENADE OL at this timepoint, if the eligibility criteria are met.

The overall study design is depicted in Figure 1.

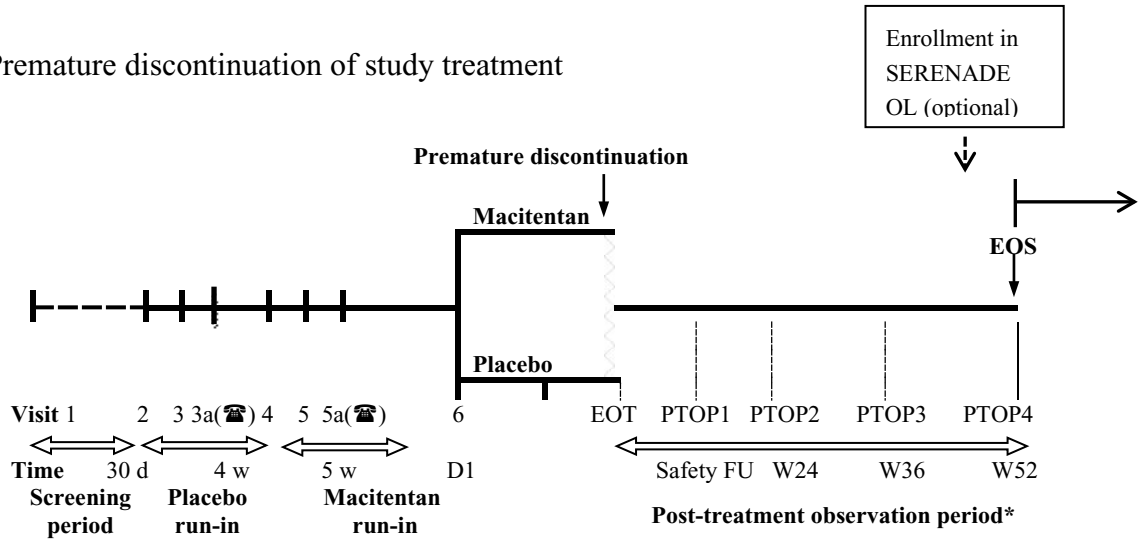
Figure 1 Study design

A) Study treatment completed as per protocol:



D = Day; d = days; EOT = End-of-Treatment; EOS = End-of-Study; W = Week; w = weeks.

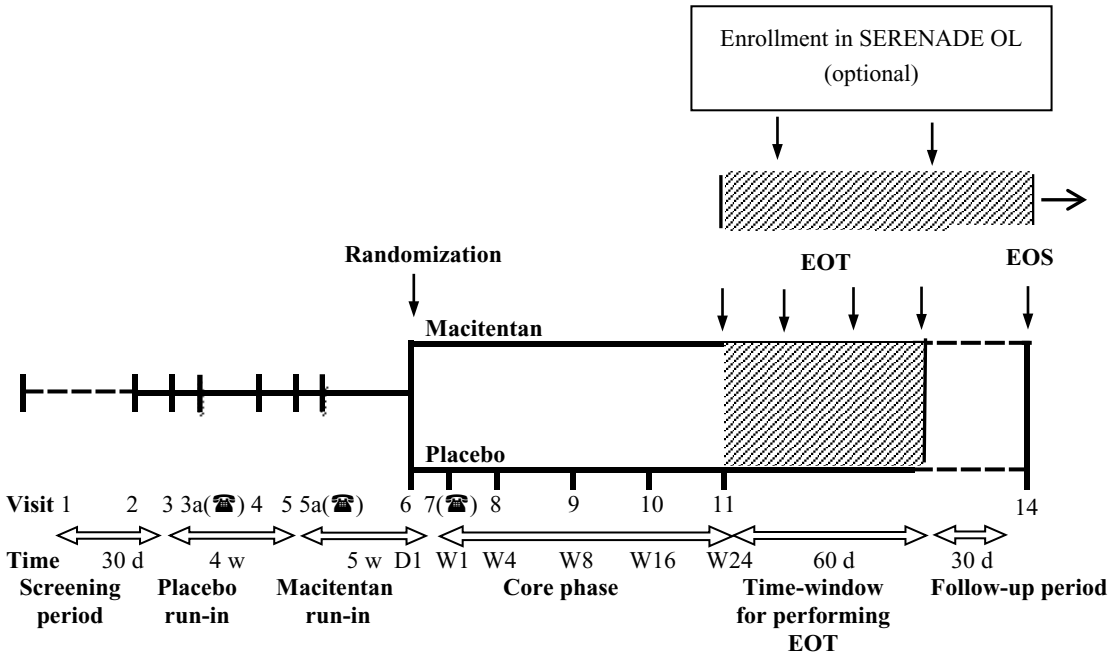
B) Premature discontinuation of study treatment



D = Day; d = days; EOT = End-of-Treatment; EOS = End-of-Study; W = Week; w = weeks.

*PTOP visits to be performed depending on the time point of premature discontinuation of study treatment. Patients who had not passed Week 24 will remain in PTOP until Week 24.

C) Discontinuation of double- blind treatment period at Week 24 or beyond, per Global protocol Version 6



D = Day; d = days; EOT = End-of-Treatment; EOS = End-of-Study; W = Week; w = weeks.

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., ICF signed) and ends with the last visit of the last subject.

The subjects will be treated for 52 weeks in addition to the run-in period of 9 weeks. Subjects who prematurely discontinue study treatment will enter a PTOP, which ends 52 weeks after randomization. For an individual subject, the study is completed with the EOS visit. The duration of participation in the study of a subject will be up to 17 months [see Section 3.1.1.8].

3.2 Study design rationale

3.2.1 Rationale for the use of placebo

No medical treatments have currently been approved for the treatment of HFpEF. Current practice guidelines are aimed at treating fluid retention, aggressively controlling hypertension, and treating comorbid conditions that contribute to decompensation. In this study, subjects are allowed to stay on their usual HF treatment; therefore, the addition of a placebo arm to the standard-of-care is considered acceptable. Furthermore, since fluid

retention is also a feature of HF itself, it is difficult to distinguish whether fluid retention is attributable to the natural progression of disease or to an effect of active treatment. Inclusion of a placebo group is the only way to reliably interpret the potential effect of macitentan on fluid retention. A placebo-controlled trial conducted in a randomized and double-blind fashion also provides the most rigorous method for evaluating the efficacy and safety of a medical treatment.

3.2.2 Placebo- and macitentan treatment run-in period

Studies with ERAs in HF have consistently shown issues with fluid retention. These events were more frequently observed early in the course of these studies, i.e., mainly within 4 weeks of treatment initiation [D-16.139, B-02.005, Mann 2010, Bakris 2010]. The early timing of fluid related AEs and HF exacerbation observed with ERAs in HF studies is not unique to this class of compounds. The beta-blocker carvedilol, for example, has been known to worsen HF in up to 44% of patients during the initiation of therapy [Krum 1995]. To mitigate these risks, some HF trials have employed a pre-randomization run-in period to exclude subjects who do not tolerate or do not respond to the study drug or are noncompliant [ANZ 1995, SOLVD 1991, Packer 1996, McMurray 2013]. Accordingly, the aim of introducing a placebo- and a macitentan run-in period in this study is thus to maximize the number of randomized subjects able to tolerate macitentan. The run-ins will also serve to exclude noncompliant subjects as medication noncompliance is a notorious precipitant of fluid decompensation in HF patients.

Placebo run-in period: Subjects who are not on optimal diuretic therapy may be more prone to developing fluid retention. During the placebo run-in period, which lasts for 4 weeks, the clinical stability of the subject will be established. If necessary, HF or other cardiovascular medications may be adapted to optimize treatment. The subjects must be on stable HF- and/or cardiovascular therapy for at least 1 week immediately prior to entering the macitentan run-in.

Macitentan run-in period: The purpose of the macitentan run-in is to identify and exclude subjects who are unable to tolerate macitentan as per criteria defined in Section 4.5, based on investigator judgment. Dose adjustment of oral diuretics and other cardiovascular medications is allowed, provided that the subject remains on stable therapy for at least 1 week immediately prior to randomization. The macitentan run-in will last for 5 weeks.

3.2.3 Rationale for the post-treatment observation period

In order to comply with the intent-to-treat principle, subjects who prematurely discontinue study treatment will be followed until Week 52 to collect information pertaining to hospitalization and mortality [see Section 3.1.1.8].

3.2.4 Rationale for the duration of the double-blind treatment period

The results of the MELODY-1 study (AC-055G201) showed a decrease in NT-proBNP of 13% compared to placebo after 8 weeks of treatment, and a further decrease to 23% compared to placebo after 12 weeks despite a relatively small sample size and absence of a minimum natriuretic peptide level requirement at study entry. Results from MELODY-1 are in line with other studies with other HF treatments which have shown that the effect on NT-proBNP occurs early, i.e., within 12 weeks after start of treatment [Solomon 2012, Rosenberg 2008]. As wall stress is the mechanical stimulus influencing BNP release, the improvement in NT-proBNP is expected to be attained by 24 weeks, reflecting improvements in cardiac structural remodeling which are likely to start manifesting by this time. Therefore, a study duration of 24 weeks is considered to be sufficient to observe an effect on NT-pro-BNP.

A treatment duration of 24 weeks is also considered to be sufficient to assess a change in key secondary endpoints such as daily physical activity and quality of life.

Originally, the double-blind treatment duration was 52 weeks in order to allow for an estimation of the potential effect size on morbidity and mortality for a potential Phase 3 study in this indication. However, due to early termination of recruitment and consequently reduced sample size, the number of WHF events is expected to be too low for a meaningful analysis of time to WHF. Furthermore, the primary endpoint (change in NT-proBNP) and the key secondary endpoints of KCCQ clinical summary score and change in physical activity assessed by accelerometry are all assessed at Week 24. Therefore, the double-blind treatment duration was reduced to 24 weeks [see Section 3.1.1.8].

3.3 Study committees

An Independent Data Monitoring Committee (IDMC) has overall responsibility for safeguarding the interests of subjects by monitoring the benefit-risk ratio and making appropriate recommendations based on all the reported data and 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.

An Independent Statistical Analysis Center (not otherwise involved with study conduct or statistical analysis) will have exclusive access to the randomization list and will generate the monitoring reports exclusively for review by the IDMC.

Both a Scientific Advisory Board and a Steering Committee are involved in the study design and will be consulted prior to and during the study for relevant medical issues and study publications.

An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) has been appointed to provide ongoing assessment and advice regarding serious hepatic AEs of special interest that require further evaluation during the study as per the ILSDRB charter.

4 SUBJECT POPULATION

4.1 Subject population description

The study will enroll male and female subjects aged 18 years or older with an established diagnosis of HFpEF and pulmonary vascular disease with or without overt RVD. The subjects must have signs and symptoms of HF requiring treatment with at least 1 diuretic of any type, and they must be in NYHA FC II or III. In order to assess the effect of macitentan on the physical activity of subjects, subjects must be ambulatory (i.e., subjects in NYHA FC IV are excluded).

To minimize the number of screening failures, it is recommended to only screen subjects who have had the diagnosis of HFpEF confirmed by a previous echocardiography.

Eligible subjects must be able and willing to give informed consent for participation in the clinical study.

4.2 Rationale for the selection of the study population

The improvements in CO and NT-proBNP observed in MELODY-1 [see Section 1.3] indicate a potential benefit of macitentan in subjects with CpcPH due to left ventricular dysfunction (LVD). ERAs have been previously tested in HFrEF and have not consistently shown clinical benefit [Kaoukis 2013]. As subjects with HFpEF comprised the majority of the MELODY-1 population, macitentan may present a potential benefit for this indication with a high unmet need due to lack of approved therapies.

Similarly to HFrEF, RVD may accompany HFpEF and this phenotype portends a poorer prognosis, including higher HF hospitalization rate, cardiovascular mortality, and all-cause mortality, irrespective of severity of PH or comorbid conditions [Zakeri 2015a]. In the subset of HFpEF patients with secondary RVD, increased right ventricular afterload could be mitigated by ERA treatment. A decrease in pulmonary vascular resistance (PVR) with macitentan is expected to alleviate right ventricular (RV) burden and consequently improve RV-pulmonary artery coupling.

ERAs, including macitentan, demonstrated efficacy and are generally well tolerated in subjects with PAH with a varied degree of RVD. In a Phase 3 study in subjects with PAH (AC-055-302 / SERAPHIN), macitentan reduced the risk of a morbidity or mortality event, improved exercise capacity, WHO FC and pulmonary hemodynamics, and reduced NT-proBNP, compared to placebo. In SERAPHIN, the presence of clinical signs of RVD did not negatively impact the treatment effect of macitentan. On the contrary, the treatment

effect of macitentan on the morbidity/mortality endpoint was greater in subjects with signs and symptoms of right HF (or mean right atrial pressure [mRAP] ≥ 12 mmHg) at baseline. Subjects with a more pronounced degree of RVD had an overall higher morbidity/mortality event rate.

It is currently unclear whether macitentan would be beneficial in patients with pulmonary vascular disease associated with advanced left heart disease, as increased PVR could be a protective mechanism against blood overflow in the lungs. This mechanism is thought to be the cause of early aggravation of patients with left HF who received epoprostenol [Califf 1997]. However, p*ost hoc* analyses conducted for a subset of SERAPHIN PAH patients with clinical traits compatible with a possibility of concomitant LVD reported a similar treatment effect compared to the overall SERAPHIN PAH population on the primary morbidity/mortality efficacy endpoint, as well as the combined endpoint of death and hospitalization due to PAH, and a similar effect on 6-minute walk test, without specific safety concerns in this patient subset. Similarly, patients with PAH and LV dysfunction in the AMBITION study with ambrisentan did not differ from the selected PAH population on the primary efficacy endpoint [Galiè 2015].

Subject selection in AC-055G202 is aimed to identify subjects with HFpEF and associated pulmonary vascular disease with and without overt RVD and tolerating macitentan, which will optimize evaluation of potential efficacy of macitentan as assessed by NT-proBNP, symptom burden and patient related outcomes in a Phase 2 study over 52 weeks of treatment.

4.3 Inclusion criteria

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

1. Signed informed consent prior to any study-mandated procedure
2. Male or female subjects ≥ 18 years of age
3. Signs or symptoms of HF requiring treatment with at least one oral diuretic (any type)
4. LVEF ≥ 40% (by echocardiography at screening)
5. NYHA FC II to III
6. Criterion removed (see footnote[4])
7. Patients with HFpEF defined as either one of the following by echocardiography at Screening:
   a. Left atrial (LA) enlargement:

[4] Inclusion criterion 6 (HF hospitalization within 12 months prior to Screening or RHC within 6 months prior to Screening showing PAWP/LVEDP > 15mmHg) was removed in Global protocol v.4.

i. Left atrial volume (LAV) > 58 mL (male) / > 52 mL (female), *or*
ii. Left atrial volume index (LAVI) ≥ 28 mL/m^2, *or*
iii. LA area > 20 cm^2, *or*
iv. LA diameter > 4.0 cm (male) / > 3.8 cm (female)

b. Left ventricular septal thickness or posterior wall thickness ≥ 1.1 cm

8. Elevated NT-proBNP / BNP: ≥ 200 / 60 pg/mL for subjects in sinus rhythm or ≥ 500 / 150 pg/mL for subjects with atrial fibrillation (AF) at any time within 3 months prior to Screening or at Screening
9. Pulmonary vascular disease or RV dysfunction meeting at least one of the following echocardiographic (at Screening) and/or RHC parameters (at Screening or from any RHC previously performed):
   a. Echocardiographic peak TR velocity > 2.8 m/s *or* invasive mean pulmonary artery pressure ≥ 25 mmHg (RHC) *or* PASP > 40 mmHg **and** evidence of RV dysfunction (TAPSE < 17 mm *or* RV fractional area change < 35% *or* RV tissue Doppler s' velocity < 9.5 cm/s)
   b. Diastolic Pulmonary Vascular Pressure Gradient (DPG) > 5 mmHg (RHC)
   c. PVR > 3 Wood Units (RHC)
10. A woman of childbearing potential [see definition in Section 4.6.1] is eligible only if the following applies:
   a. Negative pre-treatment serum pregnancy test.
   b. Agreement to undertake monthly pregnancy tests from Screening up to at least 30 days after study treatment discontinuation.
   c. Agreement to use reliable contraception [Section 4.6.2] from at least 30 days prior to Visit 2 up to at least 30 days after study treatment discontinuation

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria at any time during Screening, unless specified otherwise for individual criteria. It is not permitted to waive any of the criteria for any subject:

Disease-related

1. Any prior valid[5] measurement of LVEF < 40%

[5] An echocardiogram is considered valid if its quality is sufficient to allow accurate assessment of LVEF and if it is reflective of the true status of the subject (the investigator may use his judgement to disregard echocardiogram obtained during acute events such as AF with a rapid ventricular response, acute ischemia, etc.).

Cardiovascular comorbidities:

2. Significant unrepaired structural valvular heart disease (i.e., greater than mild aortic or mitral stenosis, and greater than moderate aortic or mitral regurgitation).
3. Hypertrophic, restrictive, and infiltrative cardiomyopathies.
4. Pericardial disease.
5. Acute coronary syndrome, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable coronary artery disease or has undergone coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) within 3 months of Screening.
6. Known indication for PCI or CABG.
7. Uncontrolled heart rate (HR) from atrial fibrillation or atrial flutter (> 110 beats per minute) as assessed by ECG.
8. History of serious life-threatening or hemodynamically significant arrhythmias, including symptomatic or sustained ventricular tachycardia or defibrillator shock within 12 month(s) of Screening.
9. History of or anticipated heart transplant or anticipated/implanted ventricular assist device.
10. Transient ischemic attack (TIA) or stroke within 3 months of Screening.
11. Systolic blood pressure (SBP) ≥ 180 mmHg[6] or diastolic blood pressure (DBP) ≥ 110 mmHg.

Other causes of right heart failure not associated with left ventricular dysfunction:

12. Significant parenchymal lung disease fulfilling any of the following:
    a. Forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC ratio) < 0.7 associated with FEV_1 < 50% of predicted value after bronchodilator administration in subjects with a known or suspected history of significant lung diseases.
    b. Known moderate or severe restrictive lung disease, e.g., total lung capacity (TLC) < 60% (predicted)
    c. Clinical suspicion of diffuse interstitial fibrosis or alveolitis, unless excluded by high resolution computed tomography (CT)
    d. Clinical suspicion of pulmonary thromboembolism within 12 months prior to Screening, unless excluded by ventilation/perfusion (V/Q) scan or computed tomography angiography (CTA)
13. Criterion removed (see footnote[7])

[6] For subjects with an SBP > 150 mmHg prior to randomization, the recommendations provided in Section 5.2.4 should be followed.

[7] Exclusion criterion 13 (BMI ≥ 45 kg/m^2) was removed in Global protocol Version 4.

14. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF.

Criteria related to macitentan use:

15. Administration of PAH-specific therapy (i.e., ERAs, prostanoids, PDE-5 inhibitors, guanylate cyclase stimulators) within 1 month prior to Screening.
16. Hypotension, i.e., SBP < 90 mmHg or DBP < 50 mmHg
17. Severe renal dysfunction with an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula
18. Known and documented severe hepatic impairment, e.g., Child-Pugh Class C.
19. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 3 × the upper limit of normal (ULN).
20. Hemoglobin < 100g/L (< 10 g/dL).
21. Plan to become pregnant or lactating.
22. Treatment with strong cytochrome P-450 3A4 (CYP3A4) inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, or St. John's wort within 1 month prior to screening.

    Treatment with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir within 1 month prior to Screening.
23. Criterion removed (see footnote[8])
24. Known hypersensitivity to macitentan or drugs of the same class, or any of the excipients (e.g., soy lecithin, lactose).

General criteria:

25. Planned or current treatment with another investigational treatment within 2 months prior to screening.
26. Inadequate control of comorbidities according to current standards of care, as per judgment of the investigator.
27. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease.
28. Known concomitant life-threatening disease with a life expectancy < 12 months.

[8] Exclusion criterion 24 (treatment with BCRP substrates) was removed in Global protocol v.4.

4.5 Run-in failure criteria

A subject must be discontinued from the study in case any of the following criteria is fulfilled at any time during the run-in period:

1. Study treatment compliance < 80%.
2. Central laboratory results showing a decrease in hemoglobin by > 50 g/L from Screening or hemoglobin < 80 g/L, or need for transfusion.
3. Significant fluid retention / worsening of HF as evidenced by one of the following:
   a. Administration of i.v. diuretics due to fluid retention
   b. Addition of high potency thiazide diuretic (metolazone, indapamide), or ≥ 100% increase in loop diuretic to a total oral dose ≥ 120 mg of furosemide equivalents/day[9]
   c. Increase in body weight by ≥ 5% or ≥ 5 kg from the value at the start of the corresponding run-in period (i.e., Visit 2 and Visit 4 for the placebo and macitentan run-in, respectively) due to fluid overload
   d. Worsening in NYHA FC
   e. Hospitalization for worsening of HF
4. Any AEs that preclude continuation based on investigator's judgment.

4.6 Criteria for women of childbearing potential

4.6.1 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,
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]),
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

The reason for not being of childbearing potential will be recorded in the Case Report Form (CRF).

[9] Furosemide equivalents: furosemide 40 mg: torasemide 20 mg: bumetanide 1 mg; ethacrynic acid 50 mg.

4.6.2 Acceptable methods of contraception

Women of childbearing potential [see definition in Section 4.6.1] must use acceptable birth control from Screening up to at least 30 days after study treatment discontinuation. Reliable contraception must be started at least 30 days prior to Visit 2.

The methods of birth control used (including non-pharmacological methods) must be recorded in the CRF.

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

If subjects decide that they want to change the form of birth control being used, they need to talk with the treating physician to be sure that another acceptable form of birth control is chosen.

4.6.2.1 Countries where macitentan is approved

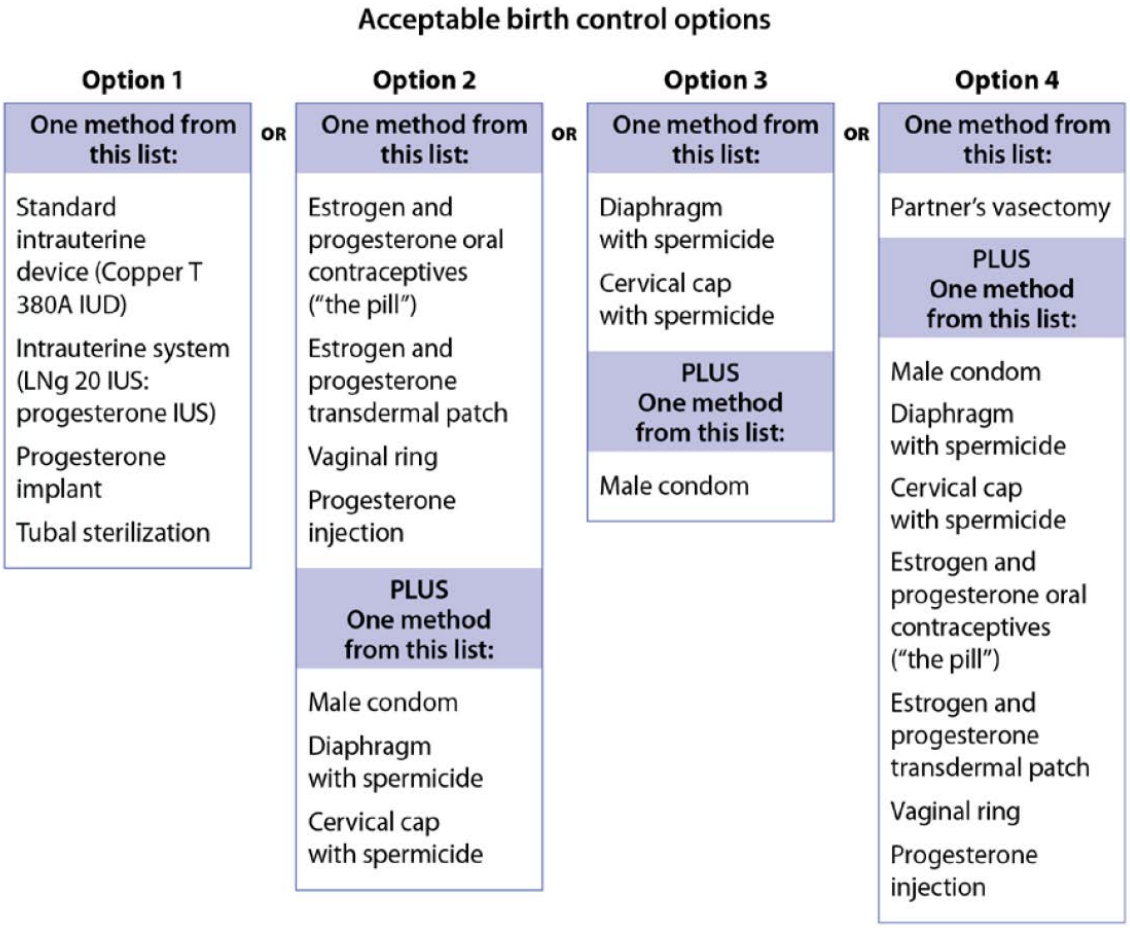
In countries where macitentan is approved, the macitentan label can be followed with respect to acceptable methods of contraception. It must be ensured that a female counselor is available to discuss this topic, if requested.

4.6.2.2 North America and countries where macitentan is not approved

Subjects may choose one highly effective form of contraception (intrauterine devices, contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods) [Figure 2]. If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method.

The investigator must counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive measures.

Figure 2 Acceptable birth control options



5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment and matching placebo: Description and rationale

Macitentan 10 mg and placebo will be provided as identical film-coated tablets debossed with '10' on one side. One tablet must be taken orally once a day.

Macitentan doses of 3 mg and 10 mg were investigated in the AC-055-302 / SERAPHIN study in subjects with PAH [Pulido 2013]. Based on the results of this trial, macitentan, at both the 3 mg and 10 mg doses, decreased the risk of a morbidity/mortality event over the treatment period versus placebo. A dose-response was identified, with the greatest efficacy demonstrated in the 10 mg dose group. Macitentan was well tolerated in this subject population. The number of AEs reported and subjects discontinuing treatment due to AEs

was similar across all groups. No differences were observed between macitentan and placebo on fluid retention (edema). For more detailed information, see the macitentan IB [Macitentan IB].

Based on these results, a dose of 10 mg was selected for the AC-055G201 / MELODY-1 study in subjects with CpcPH due to LVD. In MELODY-1, an improvement in CO and NT-pro-BNP was observed. The safety observations were consistent with the known safety profile of macitentan in other populations, and no new safety signal was detected. Therefore, a dose of macitentan 10 mg was selected as the dose for study AC-055G202.

5.1.2 Study treatment administration

The first intake of study treatment will take place at site, during Visit 2 (start of the placebo-run-in). Thereafter, one tablet must be taken orally every morning irrespective of food intake.

The subjects must be instructed not to take study treatment in the morning of study visit days. After all study assessments have been performed, a tablet from the newly dispensed bottle is taken (except at Visit 3, where the study treatment is taken from the bottle dispensed at Visit 2).

If a dose has been missed, the subject must be instructed to take it as soon as possible on the same day, and to take the next dose at the regular time. The subject must be instructed not to take 2 doses to make up for a missed dose.

5.1.3 Treatment assignment

After informed consent has been signed, the investigator/delegate contacts the Interactive Response Technology system (IRT) at Visit 1 (Screening) to obtain a subject number.

In case of re-screening, the subject number attributed at the time of first screening will also be used for the re-screened subject.

At Visit 2 (start of the placebo run-in), after having confirmed the eligibility of the subject, the investigator/delegate contacts the IRT to receive the bottle number for the placebo run-in period. At the end of the placebo run-in period (Visit 4), after having confirmed the eligibility of the subject, the investigator/delegate contacts the IRT to obtain the bottle numbers for the macitentan run-in. At the end of the macitentan run-in (Visit 6, Randomization), after having confirmed the eligibility of the subject, the IRT is contacted again by the investigator/delegate to randomize the subject. The IRT assigns a randomization number to the subject and assigns bottle number(s), which match the treatment arm assigned by the randomization list to the randomization number.

At each visit during the double-blind treatment period (except Visit 7 [telephone call], EOT and EOS), the IRT is contacted to obtain new bottle number(s). At EOT, the IRT is contacted to register the visit.

The randomization list is generated by an independent Contract Research Organization (CRO), Almac Clinical Technologies, using SAS® version 9.3.

Treatment allocation will be stratified by NT-proBNP level (≤/> 1000 pg/mL) prior to administration of the first dose of macitentan; i.e., the NT-proBNP value measured at macitentan run-in entry will be used. If the NT-proBNP value at macitentan run-in entry is not available, the NT-proBNP value measured at V1 (Screening) will be used instead. NT-proBNP is chosen as a stratification variable as it is associated with many other factors that determine outcome such as age, sex, body mass index (BMI), atrial fibrillation and chronic kidney disease.

5.1.4 Blinding

5.1.4.1 Single-blind run-in period

The placebo- and macitentan run-in periods will be performed in a single-blind fashion, i.e., only the subject is blinded to the identity of the treatment.

The investigator and site staff must exercise caution when discussing the study procedures and study treatment with the subject to keep the subject blinded to the identity of the study treatment.

5.1.4.2 Double-blind treatment period

After randomization of the subject, the study will be performed in a double-blind fashion. The investigator and study personnel, the subjects, the Clinical Research Associates (CRAs), Actelion personnel, and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until study closure. Actelion personnel responsible for clinical study supply distribution will need to be unblinded to ensure adequate supply of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file and they will not take part in any Clinical Trial Team (CTT) meetings after study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons (i.e., Global Quality Management [GQM], independent statistical analysis center and Clinical Trials Supplies Group) who are not involved in the conduct of the study.

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

5.1.5 Unblinding

5.1.5.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure, in accordance with Actelion Quality System (QS) documents.

5.1.5.2 Unblinding for interim analyses

Not applicable.

5.1.5.3 Unblinding for suspected unexpected serious adverse reactions

If 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 treatment assignment will not be communicated to site personnel or to the Actelion CTT. Unblinded SUSAR information will be provided to respective health authorities and independent ethics committees (IECs) or institutional review board (IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.5.4 Emergency procedure for unblinding

The investigator, study personnel and Actelion personnel 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 treatment assignment through the IRT. 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 unblinding with Actelion personnel.

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

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

5.1.6 Study treatment supply

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

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

5.1.6.1 Study treatment packaging and labeling

Study treatment is provided as tablets and supplied in childproof bottles containing 36 tablets each.

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

5.1.6.2 Study treatment distribution and storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label.

Unopened, sealed study treatment bottles may be stored in the refrigerator (above +2 °C [36 °F]). Storage below +2 °C / 36 °F (e.g., in the freezer) is not permitted. Opened bottles must not be stored in the refrigerator.

5.1.6.3 Study treatment dispensing

The subjects will receive sufficient study treatment (i.e., up to 4 bottles) to cover the period up to the next scheduled visit. If the study treatment is lost or damaged, a replacement bottle can be requested through the Treatment Replacement module via IRT. Subjects are asked to return all opened and unopened study treatment bottles at each visit. The protocol-mandated study-treatment dispensing procedures may not be altered without prior written approval from Actelion. Under exceptional circumstances, e.g., if study treatment is lost or damaged, or if a subject cannot return to a site within the defined time-window for a visit and does not have enough study treatment at home, the site may request permission from Actelion to send study treatment to the subject. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.6.4 Study treatment return and destruction

The protocol-mandated study treatment return procedures may not be altered without prior written approval from Actelion. Procedures for local destruction or for return and destruction by an external vendor are described in the study-specific Site Investigational Product Procedures Manual. On an ongoing basis and/or on termination of the study, the CRA will collect used and unused treatment bottles which will be sent to the warehouse, where Actelion personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by Actelion personnel or the deputy, and written permission for destruction has been obtained from Actelion.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 Study treatment accountability

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

- Dispensed bottle number(s)
- Date dispensed / number of bottles 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 tablets from the remaining study treatment bottle and to return it at the next visit.

5.1.7.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated by site personnel using the below formulas and entered in the eCRF.

Study treatment compliance calculation during the run-in period:

Placebo run-in:

$$Compliance\ (\%) = \frac{36 - n\ tablets\ returned\ at\ Visit\ 4}{n\ tablets\ that\ should\ have\ been\ taken\ between\ Visits\ 2\ and\ 4} \times 100$$

Macitentan run-in:

$$Compliance\ \ (\%) = \frac{72 - (n\ tablets\ returned\ at\ Visit\ 5\ + n\ tablets\ retuned\ at\ Visit\ 6)}{n\ tablets\ that\ should\ have\ been\ taken\ between\ Visits\ 4\ and\ 6} \times 100$$

Study treatment compliance calculation during the double-blind treatment period between 2 regular consecutive visits:

$$Compliance\ (\%) = \frac{n\ tablets\ dispensed\ \ - n\ tablets\ returned}{n\ tablets\ that\ should\ have\ been\ taken\ between\ \ 2\ regular\ visits} \times 100$$

The number of tablets that should have been taken is derived from the number of days between the day of the visit on which study treatment is dispensed (included) and the next regular visit (day of visit not included).

During the study, compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as a protocol deviation, which will be reported in the CRF by the CRA. The investigator or delegate must discuss the non-compliance with the subject to clarify the reasons and to take appropriate actions to avoid reoccurrence. This discussion and its outcome must be documented in the source documents.

5.1.8 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted.

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

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

Interruptions of study treatment must be kept as short as possible. If treatment is stopped for more than 4 consecutive weeks, re-introduction is not permitted, and treatment must be permanently discontinued [see Section 5.1.9].

Study treatment interruptions must be recorded in the CRF.

5.1.9 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Actelion personnel. The main reason and whether discontinuation of study treatment is the decision of the subject (e.g., tolerability- or efficacy-related), the investigator (e.g., due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy), or Actelion (e.g., study terminated) must be documented in the CRF. Refer to Section 3.1.1.8 for guidance on reporting the reason for study treatment discontinuation of subjects who consented to global protocol Version 6.

A subject has the right to prematurely discontinue study treatment at any time, without any justification, 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 8.2]). Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

The investigator must 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-specific criteria for discontinuation of study treatment are described in Section 5.1.10.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be asked to enter a PTOP which lasts until Week 52, provided that the subject's consent for this limited participation in the study has not been withdrawn. (The duration of PTOP for subjects who consented to global protocol Version 6 is described in Section 3.1.1.8.)

The subject will be asked to return for an EOT visit within 7 days after taking the decision to stop study treatment and for a safety follow-up visit 30 (+5) days after the last intake of study treatment (PTOP1). At the premature EOT visit, the assessments described for the regular EOT visit (Visit 13) are to be performed [Table 1]. If the premature EOT- or safety follow-up visit falls within the time-window of any of the PTOP visits, the visits can be combined.

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 is described in Sections 8.2 and 8.4, respectively.

Subjects who choose not to enter or complete the PTOP but who did not withdraw consent [see definition in Section 8.2] will be contacted by telephone at Week 52 (+/−14 days) by the site, and their vital status will be recorded in the CRF.

This does not apply to subjects who consented to global protocol Version 6.

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

5.1.10.1 Liver aminotransferase abnormalities

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

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

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

aminotransferase values return to pre-treatment levels or within normal ranges, and if the potential benefits outweigh the risks, re-introduction of study treatment can be considered. The advice of a hepatologist is recommended. Interruptions must be for less than 4 consecutive weeks; longer interruptions must lead to permanent discontinuation of study treatment.

Liver aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks and thereafter according to the recommendations in Section 7.2.4 (i.e., at monthly intervals).

Permanent discontinuation of study treatment
Study treatment must be stopped and its re-introduction 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 to ≥ 2 × ULN

Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase. 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, alcoholic hepatitis, non-alcoholic steatohepatitis, autoimmune disease) and/or etiologies (e.g., hepatic toxicity of concomitant medication[s] or other substances) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferase abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs [see Section 9].

5.1.10.2 Hemoglobin abnormalities

Hemoglobin abnormalities leading to run-in failure are described in Section 4.5.

If there is a decrease in hemoglobin from baseline[10] of > 20 g/L during the run-in or double-blind treatment period, 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:

[10] Baseline hemoglobin refers to the last hemoglobin value obtained prior to the start of the placebo run-in.

- 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.

If hemoglobin remains > 20 g/L below baseline value at subsequent visits, further re-tests are to be performed as per investigator's judgment.

This work-up should not result in study treatment interruption or discontinuation, unless clinically mandated based on the investigator's judgment, or in the following situation:

A decrease in hemoglobin to < 80.0 g/L, a decrease in hemoglobin from baseline of > 50 g/L, or the need for transfusion must result in temporary interruption of study medication, except during the run-in period where the subject must be permanently discontinued. Re-introduction of study medication can be considered if hemoglobin recovery, defined as a return of hemoglobin to within 20 g/L of the baseline value, is achieved.

Study treatment interruptions exceeding 4 consecutive weeks must lead to permanent discontinuation of study treatment.

5.1.10.3 Initiation of prohibited medications

Study treatment must be permanently discontinued if any other investigational treatments are started during the treatment period.

Treatment with strong CYP3A4 inducers and inhibitors and PAH specific drugs as detailed in Section 5.2.5 must lead to interruption of study treatment for the duration of their administration. Re-initiation of study treatment can be considered if the interruption does not exceed 4 consecutive weeks.

5.2 Previous and concomitant therapy

5.2.1 Definitions

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

A therapy that is study-concomitant is any treatment that is ongoing or initiated after signing of informed consent, or initiated up to 30 days after study treatment discontinuation.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period.

An auxiliary medicinal product is a medicinal product used for the purpose of the clinical study but not as an investigational medicinal product (e.g., a mandatory background therapy or a medicinal product used for a study-mandated procedure).

5.2.2 Reporting of previous/concomitant therapy / auxiliary medicinal products in the CRF

The use of all study-concomitant therapy (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the CRF. Previous therapy must be recorded in the CRF if discontinued less than 30 days prior to signing of the informed consent. 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 CRF.

5.2.3 Auxiliary medicinal products

All subjects must be on oral diuretic therapy (any type). On the day of the study visit, subjects will be requested to withhold their morning dose of diuretic(s) until after the blood sampling.

5.2.4 Allowed concomitant therapy

Subjects are allowed to continue with their usual HF therapy. However, HF or other cardiovascular medications must be administered at a stable dose for at least 1 consecutive week prior to entering the macitentan run-in (Visit 4) and prior to Randomization (Visit 6).

For subjects with a SBP > 150 mmHg, treatment with antihypertensives according to local guidelines [e.g., ESC Guidelines 2013, James 2014] to achieve their target BP is recommended.

After the start of the double-blind treatment period, the investigator is encouraged to keep the subject's cardiovascular medications stable, unless a change is required for medical reasons. Any change has to be recorded in the CRF as described in Section 5.2.2.

5.2.5 Forbidden concomitant therapy

The following concomitant medications are forbidden within 1 month prior to Screening and up to 30 days after study treatment discontinuation:

- PAH-specific drugs (ERAs, prostanoids, PDE-5 inhibitors, guanylate cyclase stimulators).
- Strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifabutin, rifapentin, St. John's wort).
- Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a

combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g., miconazole, piperine) until study intervention discontinuation [FDA 2020].

If subjects are currently stable on a moderate dual CYP3A4/CYP2C9 inhibitors (e.g. fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (e.g. ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (e.g. miconazole, piperine), the subject may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment. However, the subject will not be eligible to enter the OL study unless the forbidden medication is discontinued 1-month prior to OL enrollment.

- Any other investigational drug.

Initiation of ENTRESTO® (sacubitril/valsartan) is forbidden during the core phase of the double-blind treatment period.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint

- Percent of baseline NT-proBNP assessed at Week 24.

Rationale:

NT-proBNP is one of the best established cardiovascular response markers among all available surrogates in HF. Changes in this marker may reflect reduction in cardiac load and LV wall stress and reductions in NT-proBNP have been associated with improved outcomes in HF [Januzzi 2013, Grewal 2008]. NT-proBNP is a suitable endpoint for a Phase 2b, non-registration study in this indication, provided it is accompanied by an improvement in symptom burden and/or patient related outcomes (key secondary endpoints) and well characterized cardiovascular safety. NT-proBNP is simple to assess, it allows shorter study duration. Percent change in NT-proBNP was the most objective endpoint in MELODY-1 (decrease in NT-proBNP of 13% compared to placebo after 8 weeks of treatment with 10 mg macitentan once daily, and a further decrease to 23% compared to placebo after 12 weeks) despite a relatively small sample size in MELODY-1 and without minimum natriuretic peptide level requirement at study entry. This effect was commensurate with increased CO without increases in PAWP or HR. In addition, NT-proBNP has been used as the primary endpoint in a study in HFpEF (PARAMOUNT study [Solomon 2012]) of similar size and duration as study AC-055G202.

As wall stress is the mechanical stimulus influencing BNP release, the maximum improvement in NT-proBNP is expected to be attained by 24 weeks, reflecting improvements in cardiac structural remodeling which are likely to manifest by this time.

Therefore, a study duration of 24 weeks is considered to be sufficient to observe an effect on NT-pro-BNP.

The statistical method used to analyze the primary efficacy variable takes into account the expected underlying log normal distribution of NT-proBNP [Solomon 2012]. As a consequence, the treatment effect will be tested on a log-scale using a classical general linear model for normally distributed variables and expressed, on the original scale, as the ratio between treatment groups of the geometric means of individual percent of baseline at Week 24 (macitentan over placebo). As a consequence, the primary endpoint is defined for each subject as percent of baseline at Week 24.

6.1.2 Key secondary efficacy endpoints

- Change from baseline to Week 24 in the clinical summary score (as assessed by the Kansas City Cardiomyopathy Questionnaire [KCCQ]).
- Change from baseline to Week 24 in accelerometer-assessed proportion of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minute.
- Time to WHF event over 52 weeks.

Rationale for the choice of key secondary endpoints:

The effect on NT-proBNP needs to be accompanied by improvements in clinically relevant measures, such as quality of life, functional capacity, and delay in first occurrence WHF.

The KCCQ is a valid, reliable and responsive health status measure for patients with CHF and may serve as a clinically meaningful outcome in cardiovascular (CV) clinical research, patient management and quality assessment [Green 2000]. The HF symptoms and physical limitation domains scores show the best the correlation for improvements following a CHF exacerbation [Green 2000]. Thus, the key secondary endpoint is the clinical summary score (mean of physical limitation and total symptoms scores) of the KCCQ at 24 weeks. All other domains will be analyzed as other endpoints, as the instrument will be administered in its entirety.

Patients with chronic HF are characterized by a poor exercise tolerance prohibiting them to manage activities of daily living without limitation [Belardinelli 1999]. The amount of daily physical activity, as well as the intensity with which this habitual activity is performed seems important in determining functional capacity and disease severity. Accelerometer-assessed activity is a novel end point, that provides high-density quantitative data from continuous assessment of physical activity in the real-life setting, enabling a more detailed analysis of activity. With accelerometry, “every step counts” as ubiquitous walking associated with daily living seems to play a contributing role in terms of clinical prognosis. Physical activity assessed by accelerometer is significantly associated with exercise

capacity in patients with HF and is predictive of disease severity discriminating patients with mild (NYHA I) from more advanced stages (NYHA III) of HF [Jehn 2011a].

Accelerometry circumvents limitations of "targeted walking" assessed by measures such as the six-minute walk test which provides an intermittent evaluation of submaximal exercise capacity and which therefore can underestimate the true burden of HF.

Accelerometry has already been used in HF studies. The NEAT-HFpEF study represents the first study within a dedicated HFpEF population to use accelerometer-assessed physical activity as a primary end point [Redfield 2015]. Recent studies in patients with HFrEF have demonstrated correlations between accelerometer data and NYHA FC, six-minute walk distance (6MWD), peak oxygen consumption, and estimated (Seattle Heart Failure Model) or observed mortality risks. Studies have also shown increases in accelerometer-assessed activity after cardiac resynchronization therapy, confirming its ability to reflect therapeutic response [Zakeri 2015a].

Validity, analytic issues, and compliance with externally worn accelerometer devices have been addressed in clinical trials for patients with chronic obstructive pulmonary disease, among whom age and activity level are likely comparable with elderly patients with HFpEF [Lores 2006, Hecht 2009, Jehn 2011b]. In addition, physical daily activity assessed by accelerometry has been shown to correlate with 6MWD in adult PAH patients and is significantly lower in patients with WHO FC III/IV as compared to WHO FC I/II [Pugh 2012, Ulrich 2013].

WHF event is defined as an event that includes HF death, WHF hospitalization or an urgent WHF visit during which a subject exhibits new or worsening symptoms of HF, has objective evidence of WHF, and receives initiation or intensification of HF treatment [ACC/AHA 2015]. Accurate recognition of WHF events is important as they are associated with the poor outcomes and societal burden. The 2015 ACC/AHA definitions of a HF event and a HF death will ensure accurate and consistent reporting of WHF events during the study, independent of whether the exacerbation of HF results in hospitalization, recognizing that exacerbation of HF can often be managed on an outpatient basis such as with an urgent or unscheduled outpatient office/practice or emergency room visit [ACC/AHA 2015]. Using a standardized definition of a WHF event is particularly important in a global clinical trial, as standard-of-care may significantly differ across participating countries and sites. For the purposes of this study, HF death is included in the definition of WHF, in order to ensure that relevant fatal events without preceding hospitalization or an urgent/unscheduled/emergency visit are also captured.

6.1.3 Other efficacy endpoints

- Number of days alive and out of the hospital (DAOH) assessed over 52 weeks

- Time to first occurrence of the composite endpoint, which is defined as either HF death or HF hospitalization[11] over 52 weeks
- Time to first occurrence of a composite of CV death[12] or CV hospitalization[13] over 52 weeks
- Number of hospital admissions (for HF) over 52 weeks
- NYHA FC (improved/worsened/stable) at each post-baseline assessment
- Clinical composite outcome measure ('worsened', 'unchanged', 'improved') based on NYHA class, patient global assessment and occurrence of death or HF hospitalization at each post-baseline assessment
- Change from baseline in the KCCQ overall summary score as well as clinical summary score and physical limitations score over time
- Percent of baseline NT-proBNP over time
- Percent of baseline mid-regional pro-atrial natriuretic peptide (MR-proANP) over time
- Change from baseline in accelerometer-assessed physical activity variables over time:
  - Proportion of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minute
  - Mean daily number of episodes of activity over 100 activity counts per minute of at least 1-minute duration
  - Mean count per minute of daily activity
  - Mean daily number of episodes of activity over 100 activity counts per minute of at least 5 minutes duration
  - Mean daily accelerometer units
- Proportion of time spent in:
  - Sedentary physical activity
  - Light physical activity
  - Moderate physical activity
  - Vigorous physical activity

- at each time assessment.

- Change from baseline in echocardiography left and right heart function at Weeks 24 and 52 (e.g., TAPSE, LAV, septal e' velocity, PASP, E/e' ratio).

[11] See definition in Appendix 6.
[12] See definition in Appendix 5.
[13] See definition in Appendix 6.

6.2 Safety endpoints

- All-cause death up to 30 days after study treatment discontinuation
    - Number of all-cause hospital admissions up to 30 days after study treatment discontinuation
- Treatment-emergent AEs and SAEs up to 30 days after study treatment discontinuation
- AEs leading to premature discontinuation of study treatment
- Change in vital signs (systolic and diastolic arterial BP and pulse rate) and body weight up to 30 days after study treatment discontinuation
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation
- Change from baseline in eGFR up to 30 days after study treatment discontinuation
    - Decrease from baseline in SBP of ≥ 5% and SBP < 100 mmHg up to 30 days after study treatment discontinuation.

6.3 Quality of life endpoints

See key secondary endpoints [Section 6.1.2].

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 1, Table 2 and Table 4. For all visits, the subjects must be seen on the designated day with the allowed visit window indicated in Table 1, Table 2 and Table 4. If it is not possible to complete all assessments on the same day, a visit may extend to more than 1 day within the allowed time-window.

Visits 1 (Screening) and 2 (placebo run-in start) may be combined, if a local laboratory test confirms eligibility of the subject, and the locally read echocardiographic parameters meet the eligibility criteria. However, if the results from the central laboratory and central echocardiography reader do not confirm eligibility, then the subject must be discontinued from the study.

During the run-in period, 2 safety visits and 2 safety phone calls will be performed. Visits 3 and 3a (phone call) are performed 1 and 2 weeks (±2 days), respectively, after the start of the placebo run-in. Visits 5 and 5a (phone call) are performed 1 and 2 weeks (±2 days), respectively after the start of the macitentan run-in. A follow-up safety visit must be performed 30 (+5) days after intake of the last dose of study treatment, unless the subject transitions to the SERENADE OL study.

The EOT visit only applies to randomized subjects. In case of premature discontinuation of study treatment, the EOT visit must take place as soon as possible and no later than 7

days after taking the decision to stop study treatment. Subjects who prematurely discontinue study treatment or withdraw consent from further participation in the study will not be replaced.

7.1.1 Screening/re-screening

Screening starts with the first screening assessment. The date of the first screening assessment corresponds to the date of the Screening visit.

It is the responsibility of the investigator/delegate 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 and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

Subjects who are in Screening when the enrollment target has been met may still be randomized.

It is permitted to re-screen subjects twice, if the reason for non-eligibility is transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication). All screening assessments except pulmonary function tests (PFTs) must be repeated at the time of re-screening. If the screening echocardiography was done within 2 months of the re-screening visit, it does not need to be repeated.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Vital signs (BP and HR) and body weight will be measured at each unscheduled visit and recorded in the CRF. In addition, concomitant medications and AEs will be recorded, as applicable. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments (including laboratory assessments as necessary) will be performed based on the judgment of the investigator and the results will be recorded in the CRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

7.1.3 EOT and EOS in case of transition to the SERENADE OL study

The SERENADE OL enrollment visit is combined with Visit 11 (Week 24) or the EOT visit, and the EOS (safety follow-up) visit of the main study will not be performed.

In case the EOT- and SERENADE OL enrollment visit cannot be combined, subjects will enter the safety follow-up period in the main study. In this scenario, the EOT visit of the main study and the SERENADE OL enrollment visit will be 2 separate visits. The transition to SERENADE OL occurs within 30 days of the intake of the last dose of double-blind study treatment, and the EOS visit will not be performed. If transition within

30 days of intake of the last dose is not possible, then the EOS visit will be performed and eligible subjects may transition into SERENADE OL when feasible.

For subjects in PTOP, the OL enrollment visit will be combined with the corresponding visit (EOS, PTOP 2 or PTOP4, as applicable). Results of assessments applicable to both EOT (or EOS, PTOP 2 or 4) and OL enrollment visits and corresponding actions, as applicable, must be reported in the CRF of the main study.

Table 1 Visit and assessment schedule during the run-in period

PERIODS		SCREEN-ING	SINGLE-BLIND RUN-IN						Rando--mization [2]
			Placebo run-in			Macitentan run-in			
Duration		Up to 30 d	4 w			5 w			
VISITS[1]	Number	1	2	3	3a ☎	4	5	5a ☎	6
	Time		D1-R	W1-R (±2 d)	W-2R (±2 d)	W4-R (±4 d)	W5-R (±2 d)	W6-R (±2 d)	W9-R (±4 d)
Informed consent		X							
Eligibility		X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Medical history		X							
Concomitant therapy		X	X	X	X	X	X	X	X
Physical examination		X	X	X		X	X		X
Vital signs (BP, HR)		X	X	X		X	X		X
Body weight, height[4]		X	X	X		X	X		X
Home body weight monitoring[5]			←			Daily			→
PFTs[6]		X							
12-lead ECG[7]		X				X			X
Echocardiography		X							
RHC (optional)		X							
Accelerometry			X[8]	X[9]			X[9]		
NYHA FC		X	X	X		X	X		X
WHF									X
PGA / KCCQ									X
Study trt dispensing			X			X	X		X
SAEs/AEs[10]		X	X	X	X	X	X	X	X
Signs indicative of a fluid retention /HF event[11]					X			X	

[1] Unscheduled visits may be performed at any time during the study. Body weight and vital signs (BP, HR) must be performed at each unscheduled visit. Other assessments are performed at the discretion of the investigator.
[2] Subjects who are not randomized (i.e., run-in failures) must perform a safety follow-up visit 30 (+5) days after intake of the last dose of study treatment.
[3] Run-in eligibility criteria defined in Section 4.5.
[4] Body weight is measured at each visit. Height is only measured at Screening.
[5] Subjects will be instructed to monitor their body weight at home on a daily basis during the run-in period, and to contact the study site if they notice any unusual weight increase (i.e., ≥ 2 kg / 4.4 lbs) after start of study treatment.
[6] Historical PFTs accepted if performed within 1 year prior to Screening and judged reliable by the investigator, provided the subject's pulmonary status remained unchanged during this time. Only necessary for subjects with a known or suspected history of significant lung disease.
[7] ECGs are read locally only.
[8] Accelerometry will be performed from Visit 2 until Visit 3.
[9] Accelerometry will be performed during 9 days following the visit.
[10] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported [see also Section 9].
[11] During the phone calls, the investigator must inquire about signs and symptoms that may be indicative of a fluid retention- or HF event. Outcome of the phone call may trigger unscheduled visits per investigator's discretion.

AE = adverse event; BP = blood pressure; D = Day; d = days; ECG = electrocardiogram; FC = functional class; HR = heart rate; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; PGA = patient's global assessment; PFT = pulmonary function test; R = Run-in; RHC = right heart catheterization; SAE = serious adverse event; trt = treatment; W = Week; w = weeks; WHF = worsening heart failure.

Table 2 Visit and assessment schedule during the double-blind treatment period

PERIODS		DOUBLE-BLIND TREATMENT								FOLLOW-UP
		Rando-mization	Core phase					Extension phase		
Duration			24 w					28 w		30 d
VISITS[1]	Number	6	7	8	9	10	11	12	13 (EOT)[8]	14 (EOS)
	Time	D 1 (±4 d)	W1 ☎[2] (± 2 d)	W4 (± 4 d)	W8 (± 4 d)	W 16 (± 8 d)	W 24 (± 8 d)	W 36 (± 8 d)	W 52 (± 8 d)	30 (+5) d after last dose
Concomitant therapy		X	X	X	X	X	X	X	X	X
Physical examination		X		X	X	X	X	X	X	X
Vital signs (BP, HR)		X		X	X	X	X	X	X	X
Body weight		X		X	X	X	X	X	X	X
Home body weight monitoring[3]		←			Weekly				→	
12-lead ECG[4]		X		X		X	X		X	
Echocardiography							X		X	
Accelerometry[5]				X		X	X			
NYHA FC		X		X	X	X	X	X	X	X
WHF		X		X	X	X	X	X	X	X
PGA / KCCQ		X			X	X	X	X	X	
Study trt dispensing		X		X	X	X	X	X		
SAEs/AEs[6]		X	X	X	X	X	X	X	X	X

[1] Unscheduled visits may be performed at any time during the study. Body weight and vital signs (BP, HR) must be performed at each unscheduled visit. Other assessments are performed at the discretion of the investigator.
[2] Telephone call only.
[3] Subjects will be instructed to monitor their body weight at home on a weekly basis during the double-blind treatment period, and to contact the study site if they notice any unusual weight increase (i.e., ≥ 2 kg / 4.4 lbs) after start of study treatment.
[4] ECGs are read locally only.
[5] Accelerometry will be performed during 9 days following Visits 8 and 10.
[6] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported [see also Section 9].

[7] Under global protocol Version 6, accelerometry will be performed during the 9 days prior to Visit 11 (Week 24 visit).
[8] Subjects who have passed Week 24 at the time of approval of global protocol Version 6 will have their EOT visit within 60 days but no later than Week 52.

AE = adverse event; BP = blood pressure; D = Day; d = days; ECG = electrocardiogram; EOS = end-of-study; EOT = end-of-treatment; FC = functional class; HR = heart rate; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; PGA = patient's global assessment; PFT = pulmonary function test; R = Run-in; RHC = right heart catheterization; SAE = serious adverse event; trt = treatment; W = Week; w = weeks; WHF = worsening heart failure; V = Visit.

Table 3 Laboratory assessments

PERIODS		SCREENING	SINGLE-BLIND RUN-IN				DOUBLE-BLIND TREATMENT							FOLLOW-UP	Anytime
			Placebo run-in		Macitentan run-in		Core phase					Extension phase			
Duration		Up to 30 d	4 w		5 w		24 w					28 w		30 d	NA
VISITS	Number	1	2	3	4	5	6	8	9	10	11	12	13 (EOT) [8]	14 (EOS)	Fluid retention/ WHF event (any visit)
	Time		D1-R	W1-R (±2 d)	W4-R (+/−4 d)	W5-R (±2 d)	W9-R / D 1 (±4 d)	W4 (± 4 d)	W8, (± 4 d)	W 16 (± 8 d)	W 24 (± 8 d)	W 36 (± 8 d)	W 52 (± 8 d)	30 (+5) d after last dose	
Central laboratory tests[1]		X[2]			X		X	X	X[3]	X[3]	X[3]	X[3]	X	X	
Local laboratory test							X[4]								
Serum Pregnancy test[5]		X			X		X	X	X	X	X	X	X	X	
Urine Pregnancy test[5]									W 12	W20		W 28, 32, 40, 44, 48[6]			
NT-proBNP		X			X		X	X		X	X		X		X
MR-proANP					X		X				X		X		X
Biomarker					X		X				X		X		X[7]

Note: Table does not display phone calls.
[1] Hematology and clinical chemistry.
[2] Laboratory test at Screening must be performed in fasted state. Includes measurement of glucose, lipid profile and TSH levels.
[3] Monthly AST/ALT monitoring recommended. Local laboratory can be used.
[4] Hemoglobin to be measured locally at randomization to confirm run-in failure criteria not met.
[5] For women of childbearing potential only.
[6] Urine pregnancy test will be performed by the subject. The site will follow-up on the results with a telephone call.
[7] For patients who gave their consent for this blood sample only. To be drawn at the time of a fluid retention - or WHF event (any visit, including unscheduled, as applicable).
[8] Applicable to subjects who have completed Week 24 prior to global protocol Version 6 approval.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; D = Day; d = days; EOS = end-of-study; EOT = end-of-treatment; MR-proANP = mid-regional pro-atrial natriuretic peptide; NA = not applicable; NT-proBNP = n-terminal pro-brain natriuretic peptide; R = Run-in; TSH = thyroid stimulating hormone; W = Week; w = weeks; WHF = worsening heart failure; V = Visit.

Table 4 **Visit and assessment schedule for subjects entering the PTOP**

PERIODS	**Name**	**POST-TREATMENT OBSERVATION PERIOD (PTOP)**			
	Duration	**Up to 52 Weeks**			
VISITS	**Number**	**PTOP1**	**PTOP2**	**PTOP3[7]**	**PTOP4[7]**
	Name	**Safety follow-up**			**EOS**
	Time	**30 (+5) d after last dose[1]**	**Week 24[2] (±14 d)**	**Week 36[2] (± 14 d)**	**Week 52[2] (± 14 d)**
Concomitant therapy		X	X	X	X
Physical examination		X	X	X	X
Vital signs (BP, HR)		X	X	X	X
Body weight		X	X	X	X
12-lead ECG			X[3]		X
Echocardiography			X		X
Central laboratory tests		X[4]			
NT-proBNP / MR-proANP / Biomarker			X		X
NYHA functional class		X	X	X	X
WHF		X	X	X	X
PGA			X	X	X
KCCQ			X	X	X
Accelerometry			X[6]		
AEs		X			
SAEs		X	X	X	X

[1] If the safety follow-up visit falls within the time-window any of the PTOP visits, the visits can be combined.
[2] From randomization.
[3] ECGs are read locally only.
[4] Hematology and clinical chemistry, including serum pregnancy test for women of childbearing potential.
[6] Under Global protocol Version 6, accelerometry will be performed during the 9 days prior to PTOP2 (Week 24).
[7] Subjects who have passed Week 24 at the time of approval of global protocol Version 6 will have their EOS visit within 60 days but no later than Week 52.

AE = adverse event; BP = blood pressure; d = days; ECG = electrocardiogram; EOS = end-of-study; HR = heart rate; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = n-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PGA = patient's global assessment; PTOP = post-treatment observation period; SAE = serious adverse event; WHF = worsening heart failure.

7.2 Study assessments

The study assessments are listed in Table 1 to Table 4. The assessments that are mandatory during a visit are marked with an 'X'.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel) and are recorded in the CRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the CRF. The following order of assessments (if applicable) is recommended:

- KCCQ
- Patient's global assessment (PGA)
- Physical examination (including assessment of AEs/SAEs), vital signs, NYHA FC
- PFTs
- ECG
- Echocardiography
- Blood sampling.

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

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the screening of the first subject. Calibration certificates of other equipment must be available as per local requirements.

- Temperature measurement devices for study treatment storage area and freezer
- Evidence of maintenance of echocardiography equipment
- Body-weight scale.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all subjects include: age, sex, race and ethnicity. Previous hospitalization for HF (including date of last hospitalization) and number of HF hospitalizations in previous year will be recorded in the CRF.

Relevant medical history/current medical conditions (e.g., chronic and ongoing acute conditions, serious past conditions) present before signing informed consent will be recorded on the medical history page. Where possible, diagnoses and not symptoms will be recorded.

The following medical history will be captured in the CRF at Screening:

- Date of most recent HF hospitalization
- Number of HF hospitalizations within the last 12 months
- Atrial fibrillation or flutter (if present, indicate whether paroxysmal, persistent or permanent)
- Hypertension
- Diabetes mellitus type 1 and 2
- Chronic kidney disease
- Chronic obstructive pulmonary disease (COPD)
- Myocardial ischemia
- Coronary artery disease
- Sleep apnea
- Anemia.

The following signs/symptoms of special interest will be assessed at every visit as part of the physical examination:

- Peripheral edema (defined as increased tissue fluid indicated by perceptible pitting indentation on lower leg, foot, or sacrum after palpation)
- Pulmonary rales/crackles/crepitations
- Abdominal distention or ascites (in the absence of primary hepatic disease)
- S3 gallop
- Nocturia
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Nocturnal cough
- Jugular venous distention
- Hepatojugular reflux.

For subjects who failed Screening, the following data will be recorded in the CRF if available:

- Date/Time of ICF signature
- Demographics (age, sex, race and ethnicity)
- Reason for screen failure and associated assessments, if applicable (e.g., PFT data in case exclusion criterion 12a is met).

7.2.2 Efficacy assessments

7.2.2.1 NT-proBNP

NT-proBNP is the primary endpoint of this study. NT-proBNP blood samples will be drawn using the central laboratory kit at the visits listed in Table 3 and Table 4. The presence of atrial fibrillation must be assessed with standard 12-lead ECGs on the day of NT-proBNP sampling, and recorded in the CRF.

The subjects will be instructed to avoid high-sodium meals and to not modify their usual diet, if possible, within 3 days prior to their visit.

Further details regarding collection, storage and shipment of the NT-proBNP blood samples are provided in the central laboratory manual.

7.2.2.2 Accelerometry

The physical activity (counts/min) of the subject is assessed via accelerometer. The accelerometer is given to the subject at Visit 2 (start of placebo run-in) and the subject will wear the device daily during waking hours until Visit 3. The period between Visits 2 and 3 is considered to be a training period, and the data collected will only be used for analysis if data collected at Visit 3 are incomplete or missing. Subsequently, the subject is instructed to wear the accelerometer for 9 consecutive days during waking hours following Visit 3, Visit 5 (macitentan run-in safety visit), Visit 8 (Week 4), and Visit 10 (Week 16), as well as for 9 consecutive days during waking hours prior to Visit 11 (Week 24; see Section 3.1.1.8). This will allow for the inclusion of data during week days and weekend days and will provide a reliable estimate of the usual physical activity of the subject. Only data collected during these periods will be used for the analysis of physical activity. Subjects will receive a reminder from the site staff (e.g., telephone call, text message) to ensure that they are wearing the accelerometer during these periods. The subject will receive a reminder prior to Week 24 to ensure the device is charged and ready to be worn 9 days prior to Week 24. The site will send the reminder to subjects to keep the device charged. The accelerometers are pre-programmed to minimize patient handling and do not display the collected data, i.e., the subjects do not have access to their activity measurements since this could influence their behavior. The investigator (or delegate) instructs subjects on how and when to wear the accelerometer (refer to the AC-055G202 Accelerometry Manual). The subjects return the device to the study site and the investigator (or delegate) transfers the data to the accelerometry central lab as described in the AC-055G202 Accelerometry Manual.

The central laboratory will read daily counts/min and will analyze duration of daytime activity and time (minutes) spent in sedentary, light, moderate, vigorous physical activity. These data are transferred to Actelion.

Accelerometer devices will be provided to the investigational site before the start of the study.

7.2.2.3 Assessment of worsening heart failure event

Occurrence of a WHF event will be assessed by the investigator using the 2015 ACC/AHA definition [ACC/AHA 2015, Appendix 4].

A WHF event includes HF death, hospitalization or an urgent visit for WHF and is defined as follows:

HF death:

Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology (note: deaths due to HF can have various etiologies, including single or recurrent myocardial infarctions [MIs], ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease).

WHF hospitalization:

- Subject is admitted to the hospital with a primary diagnosis of HF
- Length of stay is at least 24 h (or extends over a calendar date)
- Subject has A, B, and C [Table 2 and Table 4].

Urgent WHF visit:

- Subject has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF but is not admitted to the hospital
- Subject has A, B, and C* [Table 2 and Table 4].

*changes to oral diuretic therapy only in case of addition of high potency thiazide diuretic (metolazone, indapamide), or ≥ 100% increase in loop diuretic to a total oral dose ≥ 120 mg of furosemide equivalents/day.

Table 5 WHF event definition

A WHF event is defined as **HF death**, **WHF hospitalization** or **urgent WHF visit** (see definition above) and **A, B and C**

A) New or worsening HF symptoms - At least one of the following symptoms must be new or have worsened:	**B) Objective evidence of WHF** At least 2 new or worsening PE findings or 1 new or worsening PE finding and 1 new or worsening laboratory criterion	**C) Initiation or Intensification of Treatment specifically for HF** Including at least 1 of the following

• Dyspnea
• Decreased exercise tolerance
• Fatigue
• Worsened end-organ perfusion
  • Kidney
  • Lung
  • Heart
  • Brain
  • Liver
• Other symptoms of volume overload
	Physical examination (PE) findings:
	• Peripheral edema
	• Increasing abdominal distention or ascites (in the absence of primary hepatic disease
	• Pulmonary rales/crackles/crepitations
	• Increased jugular venous pressure and/or hepato-jugular reflux
	• S3 gallop
	• Clinically significant or rapid weight gain thought to be related to fluid retention
	New or worsened laboratory evidence of WHF; obtained within 24 hours of presentation:
	• Increased BNP or NT-proBNP concentrations.
	• Radiological evidence of pulmonary congestion
	• Noninvasive diagnostic evidence of HF (echocardiography, cardiac MRI, cardiac PET scan, and nuclear imaging)
	• Invasive diagnostic evidence of HF (right-sided and/or left-sided heart catheterization)
		• Augmentation in oral diuretic therapy (increase in oral diuretic dose or addition of another oral diuretic)
		• I.v. diuretic or i.v. vasoactive therapy.
		  o *Vasoactive therapy may include an i.v. inotrope, vasodilator, or vasopressor.*
		• Mechanical or surgical intervention, including:
		  o *Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart).*
		  o *Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).*

BNP = brain natriuretic peptide; HF = heart failure; i.v. = intravenous; MRI = magnetic resonance imaging; NT-proBNP = n-terminal pro-brain natriuretic peptide; PE = physical examination; PET = positron emission tomography; WHF = worsening heart failure.

7.2.2.4 Clinical composite outcome measure

The variable related to this assessment will be derived by Actelion from the data reported for NYHA class and patient global assessment including death and HF hospitalization. The patient global assessment and the NYHA class are assessed as described below. The reporting of HF hospitalization is described in Appendix 6.

7.2.2.4.1 Patient global assessment

The PGA is a seven-point patient self-evaluation scale, which will be conducted at visits described in Table 2 and Table 4. At Visit 6 (randomization), the investigator/delegate will ask the subject how he/she feels about his/her condition at that time, and explains that he/she will be asked periodically to rate how he/she feels compared to this point in the study. Subsequently, subjects will be asked to rate how well they feel compared to Visit 6 (randomization/baseline); i.e., by indicating whether their clinical status has markedly, moderately or slightly improved, remained unchanged, or had slightly, moderately or markedly worsened since the start of the double-blind treatment period at Visit 6.

7.2.2.4.2 NYHA FC

The NYHA FC is one of the most reliable instruments for rating HF subjects' functionality. NYHA FC is evaluated at all scheduled visits.

NYHA class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

7.2.2.5 Echocardiography

Standard 2D/Doppler echocardiography is performed at the visits listed in Table 1, Table 2, and Table 4.

All echocardiographies will be submitted to a central echocardiography laboratory for evaluation of echocardiographic parameters outlined in the echocardiography imaging manual.

All echocardiographic parameters will be read centrally by the echocardiography laboratory and will be transferred electronically to Actelion's clinical database.

The LVEF, LA enlargement parameters, LV septal/posterior wall thickness, parameters of RV dysfunction (see inclusion criterion 9) measured centrally at Screening will determine the subject's eligibility to enter the study. If the results from the central reader cannot be awaited for logistical reasons and the locally read echocardiographic parameters meet the eligibility requirements, the subject may start the placebo run-in. However, if the locally-read results are not confirmed by the central reading results when they become available, the subject must be discontinued from the study as soon as possible as long as he/she is still in run-in. All efforts must be made to confirm eligibility before the subject enters the macitentan run-in.

If the quality of the echocardiography does not allow assessment of critical measurements (i.e., measurements listed in inclusion criteria 4, 7 and 9, septal E/e' ratio, lateral e' velocity, septal e' velocity), it may be repeated during Screening or placebo-run-in (if the subject entered run-in at risk).

All echocardiography assessments performed for the study must be reviewed by the investigator or delegate, and appropriate action must be taken in the event of safety-related findings (e.g., reporting the finding in the medical history or as an AE). Incidental findings unrelated to HF identified by central reading will be communicated to the investigator who is responsible for taking appropriate action. Subjects with clinically relevant echocardiographic findings unrelated to HF will be followed up until the final diagnosis is established and managed as per local medical practice. Detailed instructions on how to perform echocardiography and how to transfer data to the central echocardiography laboratory are provided in a separate manual.

7.2.2.6 Right heart catheterization

In order to establish the diagnosis of pulmonary vascular disease, a RHC may be performed during the Screening period, if deemed necessary by the investigator. Local guidelines will be followed.

7.2.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs and pregnancies are described in Section 9.

7.2.3.1 Safety phone calls during the run-in period

A safety phone call will be performed 2 weeks after the start of each run-in period (i.e., Run-in Weeks 2 and 6). During this phone call, the investigator or delegate will ask the subject if he/she experienced any signs and symptoms (e.g., increase in body weight, presence of extra fluid in the body, swelling of legs, feet and ankles, increase in dyspnea

or difficulties in breathing, or increase in exercise intolerance and other cardiac symptoms [chest pain, palpitations]) that could be indicative of fluid retention or heart failure worsening. If any new signs or symptoms are reported by the subject, or if a body weight increase ≥ 2 kg / 4.4 lbs is noted, it is recommended to perform an unscheduled visit to do a medical assessment.

7.2.3.2 Physical examination

Physical examination at Screening and EOT includes the examination of the general appearance, heart, lungs, abdomen, skin, extremities/peripheral vascular assessment, eyes, ears, nose, throat, neck (including thyroid), and lymph nodes. At interim visits, a more focused/shorter physical exam will include the examination of general appearance, heart, lungs, abdomen and extremities. If indicated, based on medical history and/or symptoms, additional exams may be performed as per investigator's discretion.

It is recommended that evidence of pulmonary congestion is sought if clinically indicated (e.g., chest X-ray, pulmonary ultrasound).

Information for all physical examinations must be included in the source documentation at the study site. The observations should be reported according to body system in the CRF as either normal or abnormal. If an abnormality is found it should be specified on the corresponding CRF page (except for abnormalities already reported on the specific signs/symptoms form), describing the signs related to the abnormality (e.g., fever) and not the diagnosis (e.g., pneumonia). Clinically relevant findings (other than those related to left HF and RVD) that are present prior to signing of informed consent must be recorded on the Medical History CRF form. Significant physical examination findings made after signing of informed consent, which meet the definition of an AE [Section 9.1.1], must be recorded on the AE form of the CRF.

7.2.3.3 Vital signs

Vital signs are measured at all visits. Triplicate SBP and DBP and radial pulse measurements will be measured in a supine or sitting position. It is recommended to allow the subject to rest for at least 5 minutes prior to the first reading, to perform the triplicate measurements at least 2 minutes apart, and to use the same device, same position (supine or sitting), same arm, same operator and appropriate cuff size throughout the study for an individual subject.

7.2.3.4 Weight and height

Height will be measured at Screening for BMI calculations. Body weight will be measured at the site at all visits. It is recommended to always weigh individual subject under similar conditions, i.e., indoor clothing without shoes, same scale, similar interval between weighing and last meal.

7.2.3.5 Home body weight monitoring

Subjects will be instructed to monitor their body weight at home on a daily basis during the entire run-in period and on a weekly basis during the double-blind treatment period, and to contact the study site if they notice a weight increase of ≥ 2 kg / 4.4 lbs after the start of treatment. It is recommended that the subjects always weigh themselves under similar conditions, e.g., every morning before breakfast. The subjects will receive a weight card on which body weight measurements can be recorded manually and must be instructed to bring the card along at each visit.

7.2.3.6 Pulmonary function tests

Post-bronchodilator PFTs (FEV_1 and FVC) will be performed at Screening for subjects with a known or suspected history of significant lung disease. Historical PFT data obtained within 12 months prior to Screening are accepted, provided there is evidence in the source documentation that the subject's pulmonary status has been stable/unchanged during this time and the results are considered to be reliable by the investigator.

Predicted normal values for FEV_1 and FVC will be used to determine eligibility.

Measured FEV_1 and FVC values (including historical) will be collected in the CRF. Calculated FEV_1/FVC and FEV_1 % of predicted value used by the site to assess subjects' eligibility will also be collected in the CRF.

7.2.3.7 ECG assessment

A standard 12-lead ECG is performed as indicated in Table 1, Table 2, and Table 4.

The ECG will be interpreted locally, and the presence of atrial fibrillation or atrial flutter (i.e., atrial fibrillation, atrial flutter or sinus rhythm) will be recorded in the CRF.

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

Hematology and chemistry tests will be performed at the visits indicated in Table 3 and Table 4. Monthly AST/ALT monitoring is recommended.

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.

If monthly AST/ALT monitoring in between visits is performed, a local laboratory can be used. If the local laboratory results show an increase in AST/ALT ≥ 3 × ULN, the subject must return to the site and the AST/ALT re-test must be performed centrally.

If the results from the central laboratory sample drawn at Screening are not available at the time of starting the placebo run-in phase, an additional blood sample may be drawn to verify eligibility based on a local laboratory test. The local laboratory results (with the corresponding normal ranges) must be recorded in the CRF.

At randomization, hemoglobin (run-in failure criterion, see Section 4.5) will be assessed locally to confirm eligibility of the subject.

Other exceptional circumstances that will require recording of local laboratory results of the parameters listed in Section 7.2.4.2 (with corresponding normal ranges) include hospitalization of the subject due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If two or more consecutive central laboratory samples are lost 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 personnel and the concerned site personnel. Alert flags that will trigger such notifications are displayed in Appendix 2.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate within 10 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 signing of informed consent must be recorded on the Medical History page of the CRF. Any clinically relevant laboratory abnormalities detected after signing of informed consent must be reported as an AE or SAE as appropriate [see Section 9], 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.

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

7.2.4.2 Laboratory tests

At Screening, the laboratory tests will be performed in fasted state in order to characterize the subjects in terms of their glucose levels and lipid profiles. At subsequent visits, the subjects do not need to be fasted prior to the laboratory tests.

The amount of blood collected during the study from an individual subject is approximately 150 mL (10 mL for hematology/clinical chemistry, including pregnancy test, if applicable;

3 mL for NT-proBNP, 3 mL for MR-proANP and 3 mL for the biomarker sample). For details, please refer to the laboratory manual.

Hematology

- Hemoglobin (SI Unit: g/L; Conventional unit: g/dL)
  - Hematocrit (SI Unit: L/L; Conventional unit: %)
  - Erythrocyte count (reticulocyte count) (SI Unit: 10^{12}/L; Conventional unit: 10^6/µL)
  - Leukocyte count with differential counts (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
  - Platelet count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)

Clinical chemistry

- ALT (U/L)
- AST (U/L)
- Alkaline phosphatase (U/L)
- Total and direct bilirubin (SI unit: µmol/L; Conventional unit: mg/dL)
- Creatinine (SI unit: µmol/L; Conventional unit: mg/dL)
- Blood urea nitrogen, BUN (SI unit: mmol/L; Conventional unit: mg/dL)
- Uric acid (SI unit: µmol/L; Conventional unit: mg/dL)
- Glucose (SI unit: mmol/L; Conventional unit: mg/dL)[14]
- Thyroid stimulating hormone, TSH (SI unit: mIU/L; Conventional unit: µIU/mL) [14]
- T3, T4[14]
- Lipid profile (SI unit: µmol/L; Conventional unit: mg/dL) [14]:
  - low-density lipoprotein (LDL) cholesterol
  - high-density lipoprotein (HDL) cholesterol
  - very low-density lipoprotein (VLDL) cholesterol
  - total cholesterol
  - triglycerides
- Sodium, potassium, chloride, calcium, magnesium (mmol/L)
- Total protein, albumin (SI unit: g/L; conventional unit: g/L)
- Albumin / Globulins ratio
- GFR (mL/min/1.73m^2), using the MDRD formula

Cardiac biomarkers

- MR-proANP

[14] Only measured at Screening; screening labs are measured in fasted state.

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed at Visits 1 (Screening), 4, and 6 (Randomization) and at all regular post-randomization visits [Table 3]. During the double-blind treatment period, women of childbearing potential must perform urine pregnancy tests at home in between visits at Weeks 12, 20, 28, 32, 40, 44, and 48 in addition to the serum pregnancy test during site visits. The subjects will be provided with validated urine pregnancy tests kits by the site. The investigator/delegate will follow-up on the results of the urine pregnancy test with a telephone call and records the result of the test in the CRF. If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

7.2.5 Quality of life assessments

The KCCQ will be completed at the visits indicated in Table 1, Table 2, and Table 4. It is recommended that the KCCQ be completed prior to any other clinical assessment or interaction with site staff to avoid potential bias in the subject's responses.

The KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. On average, it requires 4–6 minutes to complete.

The KCCQ is available in a number of validated translations. The questionnaire will not be administered if it is not available in a language that can easily be understood by the subject. The paper questionnaire completed by the subject is considered to be the source document. The data from the paper questionnaire will be manually entered in the CRF by site staff.

Actelion Pharmaceuticals Ltd has been granted a license agreement for the use of the KCCQ.

7.2.6 Biomarkers

A blood sample for analysis of additional exploratory protein biomarkers related to modulation of heart function and target engagement and markers which are important for the regulation of the fluid status will be collected from subjects who gave their consent for this blood sample.

The biomarker analysis will be performed after study closure and will not be included in the study report. The aim of this analysis is to investigate the effect of macitentan on proteins involved in the pathophysiology of HFpEF and pulmonary vascular disease, and to gain a better understanding of the mechanism by which ERAs contribute to fluid retention. Such markers may include, but are not limited to, galectin-3, co-peptin and biomarkers related to the renin-angiotensin system (additional biomarkers may be included in the analysis, if scientific rationale has become available through new research).

The biomarker blood samples will be drawn using the central laboratory kit at the timepoints indicated in Table 3, as well as at the time of a fluid retention - or WHF event. This includes fluid retention[15]- or WHF events[16] detected at regular or unscheduled study visits at the site.

Blood sampling procedures, storage and shipment of the biomarker samples are described in the central laboratory manual. The biomarker samples will be transferred to an Actelion designated biobank when the study is closed and may be stored there for a maximum of 15 years. Subjects may request that these samples be destroyed at any time during or after the study.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

A subject who completes 52 weeks of follow-up (± time-window indicated in Table 2 or Table 4) including the safety follow-up period is considered to have completed the study as per protocol, regardless of whether he/she has completed the double-blind treatment period as per protocol. Subjects who die are considered to have completed the study.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the CRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. 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, email 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 CRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post

[15] A fluid retention event refers to an AE related to edema or fluid overload.

[16] See definition in Section 7.2.2.3.

to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel 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 (if known) for premature withdrawal from the study, along with who made the decision (subject, investigator, or Actelion personnel) must be recorded in the CRF, if known.

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but it will not be collected in the CRF. 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 8.4.

8.3 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 the study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the IECs/IRBs, 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 8.4. 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 the study without prior agreement from Actelion, the investigator must promptly inform Actelion personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval / favorable opinion of the study, the investigator must promptly notify Actelion personnel 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.

8.4 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.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse events

9.1.1 Definition of adverse events

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

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

AEs include:

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

Overdose, misuse, abuse of the study treatment and study treatment errors will be reported as an AE.

9.1.2 Intensity of adverse events

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

If the intensity of an AE worsens within a study period, the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required to be reported. If there is a worsening in intensity occurring during a subsequent study period (i.e., placebo run-in, macitentan run-in or double-blind treatment period), this must be reported in the CRF.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally 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 9.2.1]. 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 intensity assessment, determines the regulatory reporting obligations.

9.1.3 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 the investigator.

9.1.4 Reporting of adverse events

All AEs with an onset date after signing of informed consent and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the CRF.

9.1.5 Follow-up of adverse events

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

follow-up information obtained after the subject's EOS visit will not be collected by Actelion.

9.2 Serious adverse events

9.2.1 Definitions of 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 in-patient 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 not considered as SAEs:

- 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 (e.g., if a complication prolongs hospitalization).

9.2.2 Reporting of serious adverse events

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

An SAE is defined as related to 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 (e.g., discontinuation of a subject's previous treatment during a washout period, leading to exacerbation of underlying disease).

9.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after study treatment discontinuation must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the subject's EOS visit must be reported to Actelion Global Drug Safety, but it is not recorded in the CRF.

9.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to Actelion Global Drug Safety within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.2.5 Reporting and follow-up of SAEs during the PTOP

All SAEs, regardless of investigator-attributed causal relationship, that occur during the PTOP period must be reported on AE pages in the CRF and on an SAE form.

These SAEs must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the end of the PTOP must be reported to Actelion Global Drug Safety, but it is not recorded in the CRF.

New SAEs occurring after the end of the PTOP must be reported to Actelion Global Drug Safety within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.2.6 Reporting procedures

All SAEs must be reported by the investigator to Actelion Global Drug Safety within 24 hours of the investigator's first knowledge of the event.

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

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

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. Actelion Global Drug Safety personnel 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 expectedness of an adverse reaction is determined by Actelion in the reference safety information (RSI) section provided in the most recent version of the IB. Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR and must be reported by Actelion to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.3 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.

9.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring after study start (i.e., signing of informed consent) up to 30 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to Actelion Global Drug Safety (see contact details provided on the Pregnancy form), and on an AE page in the CRF.

9.3.2 Follow-up of pregnancy

Any pregnancies must be followed up to their conclusion and the outcome must be reported to Actelion Global Drug Safety.

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 CRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.2.2.

9.4 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific 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). In addition, an IDMC is monitoring safety data [see Section 3.3]. Actelion may request additional anonymized data pertaining to the diagnostic work-up of an AE or SAE (e.g., ECGs, medical imaging, local laboratory values) for the purpose of safety monitoring. Such additional data may be shared with external experts.

10 STATISTICAL METHODS

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

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

10.1 Analysis sets

10.1.1 Screened Analysis Set

The Screened Analysis Set includes all subjects who are screened and have a subject number.

10.1.2 Placebo run-in Set

The placebo run-in Set includes all screened subjects who enter the placebo run-in and receive at least one dose of study treatment in the single-blind placebo run-in.

10.1.3 Macitentan run-in Set

The macitentan run-in Set includes all subjects who have completed the placebo run-in, enter the macitentan run-in and receive at least one dose of study treatment in the single-blind macitentan run-in.

10.1.4 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects randomized to double-blind study treatment. In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received),
- All available data are taken into account.

10.1.5 Per-protocol Analysis Set

The Per-protocol Analysis Set (PPS) comprises all randomized subjects who received double-blind study treatment and who complied with the protocol sufficiently to allow reliable assessment of the treatment effect on the primary efficacy endpoint. Subjects are evaluated according to the study treatment they have been assigned to.

Criteria for exclusion include:

- Insufficient compliance or exposure to study drug,
- Non-protocol compliant assessment of NT-proBNP at baseline or at Week 24,
- Presence of any protocol deviation questioning the diagnosis of the studied disease.

10.1.6 Safety Set

The Safety Set includes all subjects who received at least one dose of double-blind study treatment. Subjects are evaluated according to the study treatment they actually received.

10.1.7 Sub-study Analysis Set

The Sub-study Analysis Set (SAS) includes all subjects randomized to double-blind study treatment and enrolled into the sub-study (under global protocol Version 5).

10.1.8 Usage of the analysis sets

The FAS is used for the analyses of all the efficacy variables as well as for the description of the study population at baseline [see Section 10.3.1 for baseline definition]. Unless specified otherwise, individual listings are prepared on the FAS.

The PPS is used to perform specific sensitivity analysis on the primary efficacy variable.

The Safety Set is used for the analyses of the safety variables.

The Screened Analysis Set is used for the description of subject disposition.

The placebo run-in Set is used to document the reasons leading to discontinuation of placebo run-in.

The macitentan run-in Set is used to document the reasons leading to discontinuation of macitentan run-in.

The Sub-study Analysis Set is used for presenting listings and descriptive summaries of the sub-study data (6-minute walk test and Borg Dyspnea Index). Details of the analyses will be described in the SAP.

10.2 Variables

All variables described thereafter are related to the endpoints defined in Section 6.

10.2.1 Primary efficacy variable(s)

The primary efficacy variable described here below is related to the primary efficacy endpoint described in Section 6.1.1.

The primary efficacy variable is the percent of baseline [see Section 10.3.1 for baseline definition] in NT-proBNP at Week 24.

For subjects without an available NT-proBNP value at Week 24, the last available value observed before Week 24 will be carried forward and considered for the main analysis.

Percent of baseline is calculated as the ratio of the Week 24 NT-proBNP value over baseline value, expressed in percentage.

10.2.2 Key secondary efficacy variables

Key secondary efficacy variables described here below are related to the key secondary efficacy endpoints described in Section 6.1.2.

10.2.2.1 Quality of life at Week 24

The first key secondary efficacy variable is the clinical summary score derived from the KCCQ, expressed as change from baseline to Week 24.

For subjects deceased before Week 24, the scores will be set to 0.

10.2.2.2 Accelerometer-assessed physical activity at Week 24

The second key secondary efficacy variable is the proportion of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minute, expressed as change from Baseline to Week 24.

To be considered evaluable, physical activity should have been measured for at least 4 complete days at a specific time point of assessment. A complete day is defined as a record of at least 7 hours of data (after excluding the periods when the device was apparently not worn). These limitations allow for obtaining reliable results [Robertson 2011].

10.2.2.3 Time to first occurrence of worsening of heart failure event over 52 weeks

The third key secondary efficacy variable is the time to first occurrence of WHF event.

All worsening of heart failure events occurring until EOS / open-label enrollment (OLE) are considered, irrespective of subjects compliance to assigned therapies.

Subjects without any worsening of heart failure event up to EOS / OLE are right-censored at their time of EOS or OLE.

Time to first occurrence of WHF event is expressed in days and calculated as the onset date of the first WHF event minus date of randomization plus 1 or, for censored subjects, as OLE / EOS date minus date of randomization plus 1.

Prior to global protocol Version 6 subjects were followed up to Week 52 (except where subjects prematurely discontinue study). Under global protocol Version 6, subjects are followed up to at least Week 24. For the time to first occurrence of WHF event, all events

up to the EOS / OLE for each subject are considered, regardless of their duration of follow-up.

10.2.3 Other efficacy variables

This section contains definitions of the variables related to the other efficacy endpoints outlined in Section 6.1.3.

10.2.3.1 Number of days alive and out of the hospital

The number of DAOH is calculated for each subject based on total expected follow-up time, days in hospital and days dead as follows:

The total expected follow-up time is determined as the number of days from randomization until the OLE / EOS date (for alive subjects) or until the randomization date plus 52 weeks (or plus 24 weeks [see Section 3.1.1.8]) for subjects who die during the study.

The days in hospital are obtained by adding the durations of each individual hospital stay.

The days dead are calculated for subjects who die during the study as the number of days from their death to the end of the expected follow-up (randomization date plus 52 weeks [or 24 weeks; see Section 3.1.1.8]).

Days in hospital and days dead are then subtracted from total expected follow-up time to derive DAOH for each subject.

The percentage of DAOH (%DAOH) is also calculated for each subject by dividing DAOH by total potential follow-up time.

10.2.3.2 Time to first occurrence of HF death or HF hospitalization over 52 weeks

The variable of interest is the time to first occurrence of HF death or HF hospitalization based on investigator assessment.

All HF hospitalizations and HF deaths occurring until OLE / EOS are considered, irrespective of subjects compliance to assigned therapies.

Subjects still alive at OLE / EOS and without any HF hospitalizations up to OLE / EOS are right-censored at their time of OLE / EOS.

Time to first occurrence of HF death or HF hospitalization is expressed in days and calculated as the onset date of the first HF death or HF hospitalization minus date of randomization plus 1 or, for censored subjects, as OLE / EOS date minus date of randomization plus 1.

10.2.3.3 Time to first occurrence of CV death or CV hospitalization over 52 weeks

The variable of interest is the time to first occurrence of CV death or CV hospitalization based on investigator assessment.

All CV hospitalizations and CV deaths occurring until OLE / EOS are considered, irrespective of subjects compliance to assigned therapies.

Subjects still alive at OLE / EOS and without any CV hospitalizations up to OLE / EOS are right-censored at their time of OLE / EOS.

Time to first occurrence of CV death or CV hospitalization is expressed in days and calculated as the onset date of the first CV death or CV hospitalization minus date of randomization plus 1 or, for censored subjects, as OLE / EOS date minus date of randomization plus 1.

10.2.3.4 Number of HF hospital admissions over 52 weeks

The total number of recurrent HF hospitalizations is considered for each subject, based on investigator assessment.

All hospitalizations occurring until OLE / EOS are considered, irrespective of subjects compliance to assigned therapies.

Subjects who do not experience any HF hospitalization before OLE / EOS will be considered as having 0 HF hospitalization.

10.2.3.5 NYHA FC (improved/worsened/stable) at each post-baseline assessment

It is the NYHA FC value categorized as improved, worsened or stable at every post-baseline assessment.

An improvement corresponds to a decrease in NYHA class by at least one level whereas a worsening corresponds to an increase in NYHA class by at least one level. Subjects remaining in the same NYHA class as the one reported at baseline are categorized as stable.

The proportion of subjects in each category is calculated at each post-baseline assessment based on the number of subjects with non-missing data (i.e., those having a reported value of I through IV).

10.2.3.6 Clinical composite outcome ('worsened', 'unchanged', 'improved')

The clinical composite outcome measure provides an overall evaluation of whether a subject's condition is considered to have improved, worsened, or unchanged after a pre-specified period of time defined as follows [Packer 2001]:

- **Improved:** experienced a favorable change in NYHA class or in the patient global assessment by at least one class from the baseline but did not experience death or HF hospitalization during the planned duration of treatment.
- **Worsened:** experienced death or HF hospitalization during the planned duration of treatment or reported worsening of their NYHA class or patient global assessment by at least one class compared to baseline.
- **Unchanged:** neither improved nor worsened compared to baseline.

The clinical composite outcome will be calculated and described for the different following periods of time:

- Over 8 weeks
- Over 16 weeks
- Over 24 weeks
- Over 36 weeks
- Over 52 weeks

For a given period, only the deaths and hospitalizations occurring during the studied period will be taken into account in the clinical composite outcome calculation. Similarly, the last non-missing NYHA and PGA assessments performed before or at the end of the studied period will be considered.

10.2.3.7 Quality of life scores over time

The KCCQ is used and the quality of life variables of interest are:

- Overall summary score
- Clinical summary score
- Physical limitations score

Longitudinally collected over time and expressed as changes from baseline.

For deceased subjects during the study, the scores will be set to 0 after death date.

10.2.3.8 Percent of baseline in NT-proBNP over time

The variable of interest is NT-proBNP collected longitudinally over time and expressed as percent of baseline.

10.2.3.9 Percent of baseline in MR-proANP at Week 24 and over time

The variable of interest is MR-proANP collected longitudinally over time and expressed as percent of baseline.

10.2.3.10 Change from baseline in accelerometer-assessed physical activity over time

The other accelerometer variables of interest are:

- Proportion of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minute
- Mean daily number of episodes of activity over 100 activity counts per minute of at least 1-minute duration
- Mean count per minute of daily activity
- Mean daily number of episodes of activity over 100 activity counts per minute of at least 5 minutes duration
- Mean daily accelerometer units

Longitudinally collected over time and expressed as changes from baseline.

In addition, the proportion of time spent in:

- Sedentary physical activity
- Light physical activity
- Moderate physical activity
- Vigorous physical activity

at each time point of assessment.

10.2.3.11 Change from baseline in echocardiography left and right heart function at Week 24 and Week 52

The variables of interest are listed in Section 6.1.3.

For every variable the change from baseline to Week 24 and Week 52 will be described.

10.2.4 Safety variables

Safety variables described here below are related to the safety endpoints described in Section 6.2.

The safety variables are the following:

- All-cause death up to 30 days after study treatment discontinuation
  - Number of all-cause hospital admissions up to 30 days after study treatment discontinuation
- Treatment-emergent AEs up to 30 days after study drug discontinuation
- SAEs up to 30 days after study treatment discontinuation
- AEs leading to premature discontinuation of study treatment

- Change in vital signs and body weight up to 30 days after study treatment discontinuation
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation
- Change from baseline in eGFR up to 30 days after study treatment discontinuation
- Decrease from baseline in SBP of ≥ 5% and SBP < 100 mmHg (yes/no) up to 30 days after study treatment discontinuation.

10.2.5 Other variables

10.2.5.1 Discontinuation of placebo run-in

The reasons leading to early discontinuation of placebo run-in will be described.

10.2.5.2 Discontinuation of macitentan run-in

The reasons leading to early discontinuation of macitentan run-in will be described.

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

The effect of macitentan as compared to placebo will be tested using a mixed-models analysis of covariance (ANCOVA) adjusting for the NT-proBNP evolution observed during the macitentan run-in.

The resulting p-value will be compared to an overall 2-sided type I error of 10%.

The primary and three key secondary efficacy variables will be tested at two-sided $\alpha = 0.10$, using a hierarchical testing approach to address multiplicity concern in the FAS. The secondary efficacy variables will be tested in a sequential conditional manner following the order of Section 6.1.2.

Baseline is defined as the last non-missing value observed among all measures collected during placebo and macitentan run-ins, up to the day of randomization (Visit 6). As a consequence, for the majority of subjects, it is expected to be the value observed the day of randomization (Visit 6).

10.3.2 Analysis of the primary efficacy variable

The statistical method used to analyze the primary efficacy variable takes into account the expected underlying log normal distribution of NT-proBNP [Solomon 2012]. As a consequence, the treatment effect will be tested on a log-scale using an ANCOVA and expressed, on the original scale, as the ratio between treatment groups of the geometric means of individual percent of baseline at Week 24 (macitentan over placebo).

The model is adjusting for the log of the ratio: baseline NT-proBNP over NT-proBNP value as per IRT stratification, with the aim to better control the potential unbalance between treatment groups of the NT-proBNP levels observed before entering the macitentan run-in. Such unbalance may not be fully captured by the baseline NT-proBNP value, which is expected to be the value observed on the day of randomization for the majority of subjects, and thus already influenced by macitentan. Despite the randomization stratification based on the NT-proBNP value collected at subject's entry into macitentan run-in, a continuous covariate quantifying individual NT-proBNP evolution during the macitentan run-in is deemed more sensitive and therefore more appropriate than a binary covariate based uniquely on the stratification factor.

10.3.2.1 Hypotheses and statistical model

Due to the underlying log-normal distribution of the primary efficacy variable, an analysis of covariance will be applied on log-transformed data.

y_{ij} denotes the log-transformed percent of baseline in NT-proBNP at Week 24 for subject j in treatment group i

x_{ij} denotes the log-transformed ratio: baseline NT-proBNP over NT-proBNP value as per IRT stratification, for subject j in treatment group i

TRT_i denotes for each subject the treatment group i he/she belongs to. Equal 1 for macitentan and 0 for placebo

α denotes the common intercept

e_{ij} denotes the random error term, assumed to follow a normal distribution with mean 0 and standard error σ

The model could be written:

$$y_{ij} = \alpha + \beta_1 TRT_i + \beta_2 x_{ij} + e_{ij}$$

2-sided hypotheses are focusing on the model coefficient β_1. The null hypothesis is that macitentan and placebo effects on NT-proBNP are the same. The alternative hypothesis is that the effect of macitentan on NT-proBNP differs from placebo effect.

H_0 $\beta_1 = 0$

vs

H_1 $\beta_1 \neq 0$

The null hypothesis will be tested by a 2-sided Wald test with a 2-sided significance level of 0.10.

10.3.2.2 Handling of missing data

For subjects without available NT-proBNP value at Week 24, the last available value observed before Week 24 will be carried forward and considered for the main analysis.

This approach is chosen as it is commonly used for this specific parameter [Solomon 2012] and in order to facilitate the clinical interpretation across study publications in the same indication.

A sensitivity analysis will be performed by imputing missing NT-proBNP values at Week 24 according to the reason for drop-out. In particular, subjects who died or were hospitalized for HF before Week 24 will be assigned a value significantly higher than the one assigned to subjects who have a missing value at Week 24 due to technical/administrative reason.

10.3.2.3 Main analysis

The main analysis will be performed on subjects of the FAS, according to the intent-to-treat principle.

The main analysis of the primary efficacy variable will be carried out after log-transformation using an ANCOVA adjusting for the log of the ratio: baseline NT-proBNP over NT-proBNP value as per IRT with an overall type I error of 10% 2-sided.

The treatment effect expressed as geometric means ratio and its associated 90% 2-sided confidence interval (CI) will be estimated based on the same model by inversely transforming using the exponential function the least squares mean and 90% CIs obtained in log scale.

10.3.2.4 Supportive/sensitivity analyses

The following supportive analyses are planned:

- Main analysis on PPS,
- Analysis of variance (ANOVA) on FAS without adjustment for the NT-proBNP evolution observed during the macitentan run-in,
- Main analysis imputing missing NT-proBNP values at Week 24 according to the reason for drop-out.

10.3.2.5 Subgroup analyses

In order to assess the consistency of the treatment effect across different subject subgroups for the primary endpoint, subgroup analyses are performed in the FAS according to the following demographic and baseline disease characteristics:

- Geographical area (North America, South America, Western Europe, Eastern Europe)
- Gender (Male versus Female)
- NYHA FC (II versus III)
- Atrial Fibrillation (yes/no)
- NT-proBNP (< 1000 pg/mL and ≥ 1000 pg/mL) as per IRT stratification based on macitentan run-in entry

Subgroup analyses are performed with a separate analysis for each subgroup variable using a two factor ANOVA model with treatment, subgroup and treatment-by-subgroup interaction terms.

The test of interaction is performed with 'n-1' degrees of freedom, where 'n' is the number of subgroup categories. The treatment effect, measured as a geometric means ratio, will be estimated within each level of the subgroup variable based on the ANOVA including the interaction term. Significance of the interaction terms will be tested at a 0.01 level.

Treatment effect geometric means ratio and corresponding 90% CIs for the different levels of each subgroup are presented in a forest-plot. The forest-plot is prepared as described in [Cuzick 2005] with a vertical reference line displayed at the level of the overall treatment effect for macitentan versus placebo and a vertical reference line at geometric means ratio = 1. The p-value for the interaction test is displayed on the plot for each subgroup along with the number of patients in macitentan and the number of patients in placebo within each subgroup level.

Some of the pre-specified subgroup analyses will not be conducted or categories will be combined when it is determined that there is an insufficient number of subjects in a subgroup category to produce a valid result.

Further subgroups will be added for analysis if deemed appropriate.

No multiplicity adjustment is introduced; the subgroup analysis is descriptive in nature.

10.3.3 Analysis of key secondary efficacy variable(s)

10.3.3.1 Quality of life at Week 24

The change from baseline to Week 24 in the clinical summary score will be analyzed by means of an ANCOVA adjusting for the score baseline value and for the log of the ratio:

NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Least Squares Estimates within each treatment group and between treatment groups will be displayed along with 2-sided 90% CIs and p-values.

10.3.3.2 Accelerometer-assessed physical activity at Week 24

The change from baseline to Week 24 in the proportion of time spent in light to vigorous physical activity will be analyzed by means of an ANCOVA adjusting for the variable baseline value and for the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Least Squares Estimates within each treatment group and between treatment groups will be displayed along with 2-sided 90% CIs and p-values.

10.3.3.3 Time to first occurrence of worsening heart failure over 52 weeks

The analysis of time to first occurrence of WHF will be carried out using a proportional hazards Cox model adjusting for the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Estimate of Hazard Ratio and its associated 90% CI and p-value will be displayed.

Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at relevant time points for each treatment group and displayed in both a graphical (where the number of subjects at risk is at least 10% of the total number of subjects in the analysis set) and a tabular form. In addition, the number of subjects at risk, the number of subjects censored and the number of subjects with event will be computed at each time point and for each treatment group.

10.3.4 Analysis of other efficacy variable(s)

10.3.4.1 Number of days alive and out of the hospital

For both DAOH and %DAOH, the treatment effect will be assessed by means of an ANCOVA adjusting for the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Least Squares Estimates within each treatment group and between treatment groups will be displayed along with 90% 2-sided CIs.

10.3.4.2 Time to first occurrence of HF death or HF hospitalization over 52 weeks

The analysis of time to first occurrence of HF death or HF hospitalization will be carried out using a proportional hazards Cox model adjusting for the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Estimate of Hazard Ratio and its associated 90% CI will be displayed.

Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at relevant time points for each treatment group and displayed in both a graphical (where the number of subjects at risk is at least 10% of the total number of subjects in the analysis set) and a tabular form. In addition, the number of subjects at risk, the number of subjects censored and the number of subjects with event will be computed at each time point and for each treatment group.

10.3.4.3 Time to first occurrence of CV death or CV hospitalization over 52 weeks

The analysis of time to first occurrence of CV death or CV hospitalization will be carried out using a proportional hazards Cox model adjusting for the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Estimate of Hazard Ratio and its associated 90% CI will be displayed.

Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at relevant time points for each treatment group and displayed in both a graphical (where the number of subjects at risk is at least 10% of the total number of subjects in the analysis set) and a tabular form. In addition, the number of subjects at risk, the number of subjects censored and the number of subjects with event will be computed at each time point and for each treatment group.

10.3.4.4 Number of HF hospital admissions over 52 weeks

The number of recurrent HF hospital admissions will be analyzed using a Negative binomial regression model adjusting for the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT).

Adjusted Estimates within each treatment group and between treatment groups will be displayed along with 2-sided 90% CIs, after inverse transformation using the exponential function.

10.3.4.5 NYHA FC (improved/worsened/stable) at each post-baseline assessment

The proportion of subjects having improved, having worsened or being stable will be calculated at each post-baseline assessment by treatment group. The relative risk (macitentan over placebo) will be displayed with 2-sided 90% CIs.

10.3.4.6 Clinical composite outcome ('worsened', 'unchanged', 'improved')

The proportion of subjects having improved, having worsened or being unchanged will be calculated for each period of time by treatment group. The relative risk (macitentan over placebo) will be displayed with 2-sided 90% CIs.

10.3.4.7 Quality of life scores over time

For each variable:

- Overall score
- Clinical summary score
- Physical limitations score

the change over time is evaluated, assuming a linear pattern over time, with the use of a random coefficient regression model (with random slopes and intercepts) that includes treatment, time and time-by-treatment as factors and the score baseline value as a covariate.

The random variables for this model are the subject-intercept and the subject-by-time interaction. The error term is assumed to follow a Normal distribution and the vector of the two correlated random effects is assumed to follow a bivariate Normal distribution, each with mean 0 and unstructured covariance matrix.

The treatment effect is determined by using estimated slopes for each study treatment group on the basis of the time-by-treatment interaction term. Estimates within each treatment group and between treatment groups will be displayed overall and for each study visit along with their corresponding 90% 2-sided CIs.

No imputation of missing values is planned.

Modelling adjustments, such as addition of a quadratic term or a different covariance pattern within subject, will be made in case of meaningful conflict between the predicted and the observed data.

10.3.4.8 Percent of baseline in NT-proBNP over time

The percent of baseline in NT-proBNP over time is evaluated after log-transformation, assuming a linear pattern over time, with the use of a random coefficient regression model (with random slopes and intercepts) that includes treatment, time and time-by-treatment as factors and the log of the ratio: NT-proBNP at Baseline (randomization) over NT-proBNP value before entering macitentan run-in (as per IRT) as a covariate.

The random variables for this model are the subject-intercept and the subject-by-time interaction. The error term is assumed to follow a Normal distribution and the vector of the two correlated random effects is assumed to follow a bivariate Normal distribution, each with mean 0 and unstructured covariance matrix.

The treatment effect expressed as geometric means ratio and its associated 90% 2-sided CIs will be estimated based on the same model by inversely transforming using the exponential function of the least squares means and 90% CIs obtained in log scale. Estimates within each treatment group and between treatment groups will be displayed overall and for each study visit along with their corresponding 90% 2-sided CIs.

No imputation of missing values is planned.

Modelling adjustments, such as addition of a quadratic term or a different covariance pattern within subject, will be made in case of meaningful conflict between the predicted and the observed data.

10.3.4.9 Percent of baseline in MR-proANP over time

The percent of baseline in MR-proANP over time is evaluated after log transformation, assuming a linear pattern over time, with the use of a random coefficient regression model (with random slopes and intercepts) as described in Section 10.3.4.7.

10.3.4.10 Change from baseline in accelerometer-assessed physical activity over time

For each variable:

- Proportion of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minut
- Mean daily number of episodes of activity over 100 activity counts per minute of at least 1-minute duration
- Mean count per minute of daily activity
- Mean daily number of episodes of activity over 100 activity counts per minute of at least 5 minutes duration
- Mean daily accelerometer units

the change over time is evaluated with the use of a random coefficient regression model (with random slopes and intercepts) as described in Section 10.3.4.7.

In addition, the proportion of time spent in:

- Sedentary physical activity
- Light physical activity
- Moderate physical activity
- Vigorous physical activity

will be described at each time point of assessment by calculating for each treatment group the average time spent in each category and will be displayed in both a graphical (bar plots) and a tabular form.

10.3.4.11 Change from baseline in echocardiography left and right heart function at Week 24 and Week 52

For each variable, the change over time is summarized.

10.3.5 Analysis of the safety variable(s)

All safety endpoints will be analyzed on the Safety Set. All AEs are coded with MedDRA.

10.3.5.1 All-cause death up to 30 days after study treatment discontinuation

The number and percentage of all-cause deaths occurring up to 30 days after study treatment discontinuation will be tabulated by treatment group and by:

- System Organ Class and Preferred Term within System Organ Class, in descending order of incidence within the macitentan treatment group
- Preferred Term, in descending order of incidence within the macitentan treatment group

10.3.5.2 Number of all-cause hospital admissions up to 30 days after study treatment discontinuation

The number of recurrent all-cause hospital admissions will be analyzed using a Negative binomial regression model.

Estimates within each treatment group will be displayed, after inverse transformation using the exponential function.

10.3.5.3 Adverse events

The number and percentage of subjects with at least one treatment-emergent AE / with at least one SAE / with at least one AE leading to premature discontinuation of study treatment, occurring up to 30 days after study treatment discontinuation will be tabulated by treatment group and by:

- System Organ Class and Preferred Term within System Organ Class, in descending order of incidence within the macitentan treatment group
- Preferred Term, in descending order of incidence within the macitentan treatment group

The same analysis will be performed considering the maximum intensity of reported AEs and relationship to study treatment.

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

10.3.5.4 Vital signs and body weight

Vital signs and body weight will be described over time up to 30 days after study treatment discontinuation by means of a random coefficient regression model as described in Section 10.3.4.7.

10.3.5.5 Laboratory variables

All laboratory data transferred are taken into account regardless of whether they correspond to scheduled or unscheduled assessments. All recorded assessments will be assigned to the most appropriate study visit according to the best fitting time-window for that assessment using the usual location and scale summary statistics by treatment group.

Marked laboratory abnormalities will be summarized for each laboratory variable by treatment group providing their incidence and frequency.

Absolute values and changes from baseline will be summarized over time up to 30 days after study treatment discontinuation for selected laboratory variables (erythrocytes, hemoglobin, hematocrit, AST, ALT, total bilirubin, and alkaline phosphatase).

10.3.5.6 Glomerular Filtration Rate

GFR will be described over time up to 30 days after study treatment discontinuation by means of a random coefficient regression model as described in Section 10.3.4.7.

10.3.5.7 Decrease from baseline in SBP of ≥ 5% and SBP < 100 mmHg (yes/no)

Decreases in SBP will be summarized by treatment group providing the number and percentage of subjects with, for at least one post-baseline assessment and up to 30 days after study treatment discontinuation, a percent change from baseline ≤ −5% and a SBP < 100 mmHg at the time of assessment.

10.3.6 Analysis of the Other variable(s)

10.3.6.1 Discontinuation of placebo run-in

The number and percentage of subjects who discontinued during the placebo run-in / who completed the placebo run-in will be calculated on the placebo run-in Set.

In addition, for subjects who discontinued, the main reasons for discontinuation will be displayed in descending order of incidence. All adverse events occurring during the placebo run-in will be described.

10.3.6.2 Discontinuation of macitentan run-in

The number and percentage of subjects who discontinued during the macitentan run-in / who completed the macitentan run-in will be calculated on the macitentan run-in Set.

In addition, for subjects who discontinued, the main reasons for discontinuation will be displayed in descending order of incidence. All AEs occurring during the macitentan run-in will be described.

10.4 Interim analyses

No interim analysis will be performed.

10.5 Sample size

The sample size calculation was performed using EAST version 6.4, based on the change from baseline to Week 24 in NT-proBNP, expressed as the ratio of 24-week NT-proBNP over baseline NT-proBNP due to the lognormal nature of its underlying distribution [Solomon 2012].

A number of 300 randomized subjects is adequate to detect a geometric means ratio of 0.75 (macitentan over placebo, −0.288 in log scale) corresponding to a 25% improvement with a power of 80% and a type I error of 0.10 2-sided, when considering a standard deviation (SD) of 1 in log scale and using the Wald test. The critical value expressed as geometric means ratio is 0.83.

Following closure of Screening on 27 December 2019, it is expected that approximately 140 subjects will be randomized. With a reduced sample size of 140 and the same assumptions as above, the critical value expressed as geometric means ratio is 0.76.

The originally planned sample size calculations and assumptions are presented below, with SD ranging from 0.8 to 1 and a geometric means ratio of 0.8 or 0.75.

Power	2-sided alpha	Treatment effect (ratio of geometric means)	SD (log scale)	Total number of subjects
80%	0.10	0.8	0.8	318
			0.85	359
			0.9	403
			0.95	449
			1	497
		0.75	0.8	192
			0.85	216
			0.9	243
			0.95	270
			1	**299**

The scenario highlighted in grey corresponds to the originally chosen sample size of 300 randomized subjects for this study.

The 2-sided type I error has been fixed to 0.10 due to the Phase 2b nature of this study.

The SD of 1 has been conservatively fixed based on:

- PARAMOUNT study in which the observed SD vary between 0.91 and 0.99 (baseline and Week 12)
- MELODY-1 study for which the SD is equal to 0.82 in subjects with a NT-proBNP baseline ≥ 300 pg/mL.

The targeted treatment effect of 0.75 has been chosen based on MELODY-1 study results.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timelines 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 CRF derived from source documents must be consistent with the source documents.

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

Entries recorded by the subject in the KCCQ as well as the physician-reported global assessment are considered source data. Site personnel will review and ensure completeness and readability of the subjects' entries.

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

For each subject enrolled, regardless of study treatment initiation, a CRF 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 CRF.

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On CRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to Actelion and any CROs, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other identifier. The investigator/delegate must keep a subject identification code list at the site, showing the subject/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.

11.3 Database management and quality control

CRFs will be used for all subjects. The investigators will have access to the site CRF data until the database is closed. Thereafter, they will have read-only access. The CRF 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 personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the CRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the CRF, or simply a data correction in the CRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that 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 electronically sent to Actelion. If local laboratory data are obtained, they must be entered in the CRF by the site, as defined in Section 7.2.4.1.

NT-proBNP samples will be processed through the central laboratory and the results will be sent electronically to Actelion.

As NT-proBNP is a potentially unblinding variable, appropriate data processes will be implemented to ensure the blind is preserved and integrity of the study maintained. Individual subject NT-proBNP data assessed during the double-blind phase will not be shared with the site staff and the Sponsor's study team. There are no restrictions on NT-proBNP data up to and including Visit 6.

MR-proANP data also have the potential to unblind treatment allocation and will therefore not be shared with the site staff and the Sponsor's study team until after data base closure.

Echocardiographies are read centrally and the results are transferred electronically to Actelion.

AEs are coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA™) used by 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 Actelion QS docs. After database closure, the investigator will receive the CRFs of the subjects of his/her site (including all data changes made) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

Actelion personnel 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 study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board 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 the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

A list of members participating in the IEC/IRB 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 member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study and/or legally designated representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject and/or legally designated representative to consider his or her decision to participate in the study and it

shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

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

Site personnel authorized (according to local regulation) to participate in the consent process and/or to obtain consent from the subject and/or legally designated representative will be listed on the Delegation of Authority form supplied by Actelion. A study physician must always be involved in the consent process.

The subject and/or legally designated representative and authorized site personnel listed on the Delegation of Authority form supplied by Actelion must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

A copy of the signed and dated ICF is given to the subject and/or legally designated 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 at a minimum the study reference, the subject number, the date and, if applicable, time when the subject was first introduced to the 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's family member[s]), and the information that a copy of the signed ICF was given to the subject / legally designated representative.

If the site intends 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 IEC/IRB 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 IEC/IRB, according to procedures and before subjects are recruited.

12.4 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.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-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 ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to Actelion or (overruling) local requirements.

All protocol deviations will be reported in the Clinical Study Report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

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

12.7 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 subjects' 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 CRA has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the CRF during monitoring visits.

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

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA 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 CRA 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 CRA 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.

12.8 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 SIV.

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 CRA 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 CRFs 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 CRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data-collection times.

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

The investigator agrees to cooperate with the CRA(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.

12.9 Investigator Site File

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

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

In some cases, exceptions can be discussed with the CRA 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 immediately inform Actelion.

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

12.10 Audit

Actelion's GQM 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., standard operating procedures) 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 site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

12.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

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

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

12.12 Reporting of study results and publication

Actelion will post the key elements of this protocol and the summary of results on Actelion's Clinical Trial Register and within the required timelines on publicly accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by Actelion representatives and the Coordinating Investigator (or PI for single-center studies).

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 submission to a peer-reviewed journal.

The Coordinating Investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion personnel prior to submission to a peer-reviewed journal or presentation at a congress.

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 at a congress. 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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14 APPENDICES

Appendix 1 Marked laboratory abnormalities

Laboratory abnormalities according to the most updated version of the Common Terminology Criteria for Adverse Events [CTCAE 2010].

A marked abnormality is defined based on the following list (SI units).

Parameter	LL	LLL	HH	HHH	HHHH
Hemoglobin (g/L)	< 100	< 80	Increase of > 20 g/L above ULN or above baseline if baseline is above ULN	Increase of> 40 g/L above ULN or above baseline if baseline is above ULN	
Hematocrit (L/L)	< 0.28 for females < 0.32 for males	< 0.20	> 0.60 in men > 0.55 in women	> 0.65	
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999	
Leucocytes (× 10^9 /L)	< 3.0	< 2.0	> 20.0	> 100.0	
Neutrophils (10^9/L)	< 1.5	< 1.0	NA	NA	
Eosinophils			> 5.0 × 10^9 or > 5%	NA	
Lymphocyte (10^9/L)	< 0.8	< 0.5	> 4.0	> 20.0	
AST (U/L)	NA	NA	> 3 ULN	> 5 ULN	> 8 ULN
ALT (U/L)	NA	NA	> 3 ULN	> 5 ULN	> 8 ULN
AP (U/L)	NA	NA	> 2.5 ULN	> 5 ULN	
Total bilirubin (µmol/L)	NA	NA	> 2 ULN	> 5 ULN	
Creatinine (µmol/L)	NA	NA	> 1.5 ULN or 1.5 × baseline	> 3 ULN or > 3× baseline	
Glucose (mmol / L)	< 3.0	< 2.2	> 8.9	> 13.9	
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1	

Parameter	LL	LLL	HH	HHH	HHHH
Sodium (mmol/L)		< 130	> 150	> 155	
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0	
Magnesium (mmol/L)	< 0.5	< 0.4	-	> 1.23	
Uric acid (µmol/L)	-	-	> 590	> 720	
Albumin (g/L)	< 30	< 20	-	-	
BUN (mmol/L)	-	-	> 2.5 ULN	> 5 ULN	

AP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal.

Appendix 2 Central laboratory alert flags

Central laboratory alert flags

- On top of the flags described below, at a minimum, results above the upper limit or below the lower limit of the reference range for normal subjects will be flagged.
- **Exclusionary alert value - at Screening (Visit 1):** The result is outside the study specific defined limit for inclusion in the study.

  Hemoglobin < 100 g/L
  AST ≥ 3 × ULN
  ALT ≥ 3 × ULN
  Serum pregnancy test positive

- **Exclusionary alert value - during Run-in (Visits 2–5):** The result is outside the study specific defined limit for inclusion in the study.

  Decrease in hemoglobin by > 50 g/L from Screening
  Hemoglobin < 80 g/L
  Serum pregnancy test positive

- **Total bilirubin flag alert value - all visits:** In combination with ALT and/or AST ≥ 3 × ULN, study treatment should be stopped or not initiated.

  Total bilirubin ≥ 2 ×ULN

- **Interruption or permanent discontinuation of study medication - All visits except Screening (Visit 1), EOT and EOS:** Please refer to the study protocol; study medication must be interrupted or stopped [see Section 5.1.10].
  - AST ≥ 3 × ULN
  - ALT ≥ 3 × ULN

  AST ≥ 8 × ULN
  ALT ≥ 8 × ULN
  Serum pregnancy test positive
  Hemoglobin < 80 g/L
  Hemoglobin > 50 g/L decrease from baseline

- **Repeat alert value - all visits except Screening (Visit 1), Visit 2, and EOS:** Repeat testing is needed (+ interrupt study medication in case of ALT and/or AST ≥ 3 × ULN).
  AST ≥ 3 × ULN
  ALT ≥ 3 × ULN
  Hemoglobin > 20 g/L decrease from baseline

Appendix 3 Kansas City Cardiomyopathy questionnaire (KCCQ)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	**Extremely Limited**	**Quite a bit Limited**	**Moderately Limited**	**Slightly Limited**	**Not at all Limited**	**Limited for other reasons or did not do the activity**
Dressing yourself	○	○	○	○	○	○
Showering/Bathing	○	○	○	○	○	○
Walking 1 block on level ground	○	○	○	○	○	○
Doing yardwork, housework or carrying groceries	○	○	○	○	○	○
Climbing a flight of stairs without stopping	○	○	○	○	○	○
Hurrying or jogging (as if to catch a bus)	○	○	○	○	○	○

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become...

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
○	○	○	○	○	○

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
○	○	○	○	○	○

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○	○	○

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
○	○	○	○	○	○

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○	○	○

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
○	○	○	○	○	○

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
○	○	○	○	○

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
○	○	○	○	○

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
○	○	○	○	○

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **Quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
○	○	○	○	○

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
○	○	○	○	○

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
○	○	○	○	○

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Severely** limited	Limited **Quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	○	○	○	○	○	○
Working or doing household chores	○	○	○	○	○	○
Visiting family or friends out of your home	○	○	○	○	○	○
Intimate relationships with loved ones	○	○	○	○	○	○

Appendix 4 Worsening Heart Failure Event definitions [ACC/AHA 2015]

New or worsening symptoms - definitions

Dyspnea	Includes dyspnea on exertion, dyspnea at rest, orthopnea, and paroxysmal nocturnal dyspnea.
Decreased exercise tolerance	Decreased exercise tolerance: reduced ability to withstand or participate in activities that induce physical or mental exertion.
Fatigue	Unusual tiredness and inability to perform usual activities.
Worsened end-organ perfusion	Decreased blood supply to the vital organs (kidney, liver, lungs, heart, and brain).
Volume overload	Excessive accumulation of intravascular fluid resulting from compromised regulatory mechanisms.

New or worsening Physical Examination findings - definitions

Peripheral edema	Increased tissue fluid indicated by perceptible pitting indentation on lower leg, foot, or sacrum after palpation.
Increasing abdominal distention or ascites	Intra-abdominal fluid accumulation as determined by physical examination (in the absence of primary hepatic disease).
Pulmonary rales/crackles/ crepitations	Pulmonary rales/crackles/crepitations: Abnormal breath sounds caused by the accumulation of fluid in the lungs.
Increased jugular venous pressure and/or hepatojugular reflux	Increase in the estimated height of the mean jugular venous waveform above the right atrium in centimeters. Note: When expressed as centimeters without further description, the number should be recorded as written. When it is expressed as centimeters above the sternal angle, 5 cm should be added to the number recorded. In the absence of a numerical estimate of jugular venous pressure, "JVD", "distended neck veins," and "halfway to the jaw" or "to the angle of the jaw" would be recorded as positive for elevated jugular venous pressure.
S3 gallop	Presence of an S3 mid-diastolic heart sound.
Clinically significant or rapid weight gain	Weight gain thought to be related to fluid retention.

New or worsening laboratory data - definitions

Increase in HF biomarker	Biomarker increase BNP/NT-pro BNP with decompensation of HF (such as BNP > 500 pg/mL or NT-proBNP > 2000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase above baseline is required.
Radiological evidence of pulmonary congestion	Radiological evidence of pulmonary congestion: imaging findings consistent with increased intravascular blood volume in the lungs.
Noninvasive diagnostic evidence of HF	Noninvasive diagnostic evidence of HF: Noninvasive diagnostic evidence of clinically significant elevated left or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased LVOT minute stroke distance (TVI).
Invasive diagnostic evidence of HF	Invasive diagnostic evidence with right-sided catheterization of heart showing a PAWP (pulmonary artery wedge pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2.

HF event treatment intensification - definitions

Augmentation of oral diuretic therapy	Initiation or intensification of orally administered medication(s) that promote diuresis to treat HF.
Intravenous diuretic, inotrope, vasopressor, or vasodilator therapy	Initiation or intensification of medication(s) administered by vein to treat HF, increase production of urine, increase cardiac performance, and/or reduce cardiac preload or afterload.
Mechanical or surgical intervention	Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart) or mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

BNP = brain natriuretic peptide; HF = heart failure; JVD = jugular venous distension; LVOT = left ventricular outflow tract; NT-proBNP = n-terminal pro-brain natriuretic peptide; PAWP = pulmonary artery wedge pressure; TVI = time velocity integral.

Appendix 5 Classification of cause of death

Definitions of cardiovascular death:

Since Cardiovascular (CV) death is part of a composite efficacy endpoint, it is important to accurately classify the cause of death. CV death is defined as death with the following primary cause [ACC/AHA 2015]:

Acute MI	Death by any cardiovascular mechanism (arrhythmia, sudden death, HF, stroke, pulmonary embolus, PAD) within 30 d after an acute MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable (attributable) mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs within 30 d of an acute MI, it will be considered a death due to MI. Note: Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (PCI or CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to a cardiovascular procedure.
Sudden cardiac death	Death that occurs unexpectedly and not within 30 d of an acute MI. Note: Sudden cardiac death includes the following scenarios: • Death witnessed and occurring without new or worsening symptoms • Death witnessed within 60 min of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI • Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic recording, witnessed on a monitor, or unwitnessed but found on ICD review)

	• Death after unsuccessful resuscitation from cardiac arrest (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest) • Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology • Unwitnessed death in a subject seen alive and clinically stable ≤ 24 h before being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the patient's clinical status preceding death should be provided if available) Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 h before being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 24 h of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed but who had not been seen by family members for > 24 h).
HF	Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology. Note: Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
Stroke	Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Note: Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
CV procedure	Death caused by the immediate complication(s) of a Cardiovascular procedure.
CV hemorrhage	Death related to hemorrhage such as a nonstroke intracranial hemorrhage (e.g., subdural hematoma) nonprocedural or nontraumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
CV: other	Cardiovascular death not included in the above categories but with specific, known cause (e.g., PE, PAD).

CABG indicates coronary artery bypass graft; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention and PE, pulmonary embolism.

Appendix 6 Definition of HF and CV hospitalization

HF hospitalization is defined as:

- Subject is admitted to the hospital with a primary diagnosis of HF.
- Length of stay is at least 24 h (or extends over a calendar date).

CV hospitalization is defined as:

- Subject is admitted to the hospital with a primary diagnosis of HF, MI, stroke, resuscitated sudden death, CV procedure, CV hemorrhage or cardiovascular hospitalization not included in the above categories but with specific, known cause (e.g., PE, PAD).
- Length of stay is at least 24 h (or extends over a calendar date).

Appendix 7 Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is directly before the Table of Contents. Summary of previous amendment is provided below.

Amendment	Date	Main reason(s)
1	08 February 2017	Implementation of additional safety monitoring measures post-macitentan first dose, as requested by the FDA.
2	12 April 2017	Addition of medications mainly transported by BCRP to the list of forbidden medications, as requested by the FDA.
3	10 April 2018	Description of the transition to the SERENADE OL extension study, revision of the eligibility and run-in failure criteria and introduction of a Clinical Event Committee.
4	08 March 2019	Addition of the 6-minute walk distance sub study to assess the change in exercise capacity from baseline and the removal of the 8-hour post-macitentan first dose safety monitoring period at the start of macitentan run-in. Addition of 2 phone calls to ensure adequate safety follow-up is established during the run-in phase. In addition, the testing hierarchy of the key secondary efficacy endpoints was changed.
5	06 February 2020	• The early termination of recruitment into the study since the study failed to meet subject recruitment targets and completion of the study within reasonable timeline is not realistic. The

Amendment	Date	Main reason(s)
		sample size was updated to reflect the early termination of recruitment. • To reduce the length of the double-blind treatment period to 24 weeks. The rationale for this change is that Week 24 is the pre-defined timepoint for assessing the primary endpoint, as well as the key secondary endpoints. The secondary endpoint of time to worsening heart failure (WHF) event however was planned to be assessed up to Week 52 to gather meaningful information for the preparation of a pivotal clinical trial development program. Due to the reduced sample size, the number of WHF events is expected to be too low for a meaningful analysis of time to WHF. The double-blind treatment period will thus be stopped at Week 24, and eligible subjects will be able to transition to SERENADE OL at this timepoint. Subjects who have already completed the Week 24 visit, will be scheduled to come back for an EOT visit within 60 days and will proceed to enroll in the OL study, if eligible. • To remove the CEC which was appointed to review and adjudicate in a blinded fashion WHF events, the reasons for hospitalization and causes of death. The rationale is based on the reduction of the double-blind treatment period from 52 weeks to 24 weeks, coupled by the low occurrence of WHF events which will not allow for meaningful conclusions to be drawn. However, the investigator assessment of WHF events will continue. Removal of the CEC does not affect safety monitoring and therefore the decision was also endorsed by the Independent Data Monitoring Committee (IDMC). • To re-schedule accelerometry to be performed 9 consecutive days prior to Week 24 (Visit 11/PTOP2) for subjects completing week 24 (Visit 11) under Amendment 5 to ensure assessment performed on double-blind treatment. • To stop sub-study assessments (6-minute walk test and Borg Dyspnea Index), as number of subjects participating in the sub-study is too low to allow for meaningful interpretation of results. The planned analysis of sub-study data is amended to reflect the above amendment to the protocol.

Actelion Pharmaceuticals Ltd
Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A multi-center, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

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SERENADE

Macitentan in heart failure with preserved ejection fraction and pulmonary vascular disease

Protocol AC-055G202; Phase 2b

JNJ-67896062/ACT-064992 Macitentan

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

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Date: 2 July 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: D-20.203

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL [AC-055G202]

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures, eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent). The following assessments should be made and documented in the eCRF and source documents:

        - Weekly body weight measurements
        - Follow-up on ongoing AEs, recording of new AEs
        - Changes in concomitant medications
        - Results from urine pregnancy test, as applicable

    Wherever possible, the following efficacy assessments should be performed and recorded in the eCRF if they would have been assessed at the missed visit:

- Kansas City Cardiomyopathy Questionnaire: the site should administer the KCCQ by interview over the phone. When administering the KCCQ, the following points should be considered:

    - The participant should be interviewed without others in attendance. This will not only make the participant more comfortable, but also ensure that the answers are those of the participant.
    - The instructions and each part (the question and available responses) of the questionnaire should be read exactly as written.
    - If the participant does not understand the question, it should not be interpreted for them. Participants should merely be reassured that there are no right or wrong answers and that they should answer the questions as best they can. The question can be reread to the participant.

- Patient Global Assessment (PGA): The PGA can be administered by interview over the phone.
- Accelerometry: if the participant still has an accelerometer at home, he/she will be instructed to keep the device charged and to start wearing it as per ‘visit and assessment schedule’ of the SERENADE protocol. If the participant doesn’t have an accelerometer at home, the site will send an accelerometer to the participant.

- Procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration (including the potential for self-administration of study intervention). Since this is pre-planned in the protocol under exceptional circumstances (section 5.1.6.3), direct-to-subject shipments are not considered to be a protocol deviation.

- Laboratory assessments using a suitably accredited local laboratory: for selected measures (eg, urine pregnancy tests), home testing may be employed. Safety laboratory testing should include AST/ALT and hemoglobin at minimum. NT-proBNP should be measured if a visit which includes NT-proBNP sampling is missed.

- Other procedures, eg, imaging, may be conducted at an appropriate facility.

  Once the restrictions are lifted, the subject should return to the site within 4 weeks to start to perform all safety and efficacy assessments that have been missed.

  - Missed assessments/visits will be captured in Rave, electronic data capture system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF. Other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs, per addendum to the eCRF completion guidelines. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.

  - The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

Guidance for re-consenting and monitoring

- Re-consenting to protocol v.6 (core ICF v.6) can be done over the phone and/or mail; provided local regulations allow this mode of consenting.

- Remote monitoring will be performed if this can be implemented at the site, per local requirements.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): William Byrn

Institution: Janssen Research & Development

Signature: PPD _____ Date: 03 July 2020
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.