Actelion Pharmaceuticals Ltd. *
(a Janssen Pharmaceutical Company of Johnson & Johnson)

Macitentan / ACT-064992

Heart failure with preserved ejection fraction and pulmonary vascular disease

Protocol AC-055G203

SERENADE OL

A long-term, multicenter, single-arm, open-label extension of the SERENADE study, to assess the safety and efficacy of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

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Macitentan / ACT-064992
HFpEF and pulmonary vascular disease
Protocol AC-055G203 / SERENADE OL
Amendment 5 Version 6, 26 November 2020

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SPONSOR SIGNATURE PAGE

Treatment name / number

Macitentan / ACT-064992

Indication

Heart failure with preserved ejection fraction and pulmonary vascular disease

Protocol number, study acronym, study title

AC-055G203, SERENADE OL: A long-term, multicenter, single-arm, open-label extension of the SERENADE study, to assess the safety and efficacy of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

I approve this protocol.

PPD

PPD

PPD

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PPD

INVESTIGATOR SIGNATURE PAGE

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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 well-being 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	Town	Date	Signature
Principal Investigator			_____	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5, Version 6	26-November-2020
Amendment 4, Version 5	16-July-2020
Amendment 3, Version 4	06-February-2020
Amendment 2, Version 3	16-May-2019
Amendment 1, Version 2	02-August-2018
Original Protocol, Version 1	14-May-2018

Amendment 5 (26-Nov-2020)

Overall Rationale for the Amendment:

The overall reasons to issue this protocol amendment are to adapt to changed internal safety language and reporting processes to align with TransCelerate template, to update information about posttreatment access program, study treatment storage conditions, forbidden medications, Actelion's policy for study data disclosure, and to make minor editorial revisions and corrections.

A Protocol Amendment Summary of Changes Table for current amendment is provided below. The updates are indicated in bold text and strike-through for the deleted text.

Section number and Name	**Description of Change**	**Brief Rationale**
Title Page	Legal name of the organization is updated along with a note.	Logistical updates.
Synopsis; 3.1.1 Study periods; 7.1 General information; 8.1 Study completion as per protocol	Following statement is added: '**The safety follow-up visit will be waived in case the subject moves to a continued access program and in that case EOT will be the last visit in the study.**'	To update about the waiver of safety follow-up visit in case the subject moves to post treatment access.
5.1.5.2 Study treatment distribution and storage	Highly detailed study treatment storage conditions are deleted.	The text is revised to make the study treatment label as a primary reference source for storage conditions requirement and to remove the details from protocol.
5.1.5.4 Study treatment return and destruction	Information regarding proper handling, storage and destruction of unused and used study treatment at the authorized study sites as well as the corresponding documentation is updated.	To align with Janssen processes.

Section number and Name	**Description of Change**	**Brief Rationale**
5.1.9.4 Pregnancy	"Pregnancy Form" updated to "Pregnancy Notification Form"	Updated to align with Janssen processes.
5.1.10 Study treatment overdose and treatment	A new section is added.	To provide information about overdose and treatment.
5.2.4 Forbidden concomitant therapy	Following information related to forbidden medication is updated: '**Endothelin receptor antagonists (other than macitentan 10 mg)**.' '~~PAH specific drugs (ERAs, prostanoids, PDE-5 inhibitors, guanylate cyclase stimulators)~~.'	PH-specific therapies (eg, PDE-5 inhibitors) are not approved for the treatment of HFpEF-PVD; however, their use in an individual patient is based on the investigator's judgement.
8.4 Medical care of subjects after study completion / withdrawal from study	Information about post study continued access program and the subjects eligible for receiving it is updated.	To describe the continued access options after completion of SERENADE OL.
9.1.5 Follow-up of adverse events	Additional information regarding investigator's obligations to perform or arrange supplemental measurements and evaluations is added.: '**The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or product quality compliant (PQC) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.**'	To align with Janssen processes.
9.2.1 Definition of serious adverse events	Following statement is added. '• **Is a suspected transmission of any infectious agent via a medicinal product**'.	To align with TransCelerate Protocol Template.
9.2.2 Reporting of serious adverse events	Inclusion of product quality complaints (PQCs) as reportable events in addition to SAEs.	PQCs included to comply with Janssen processes.

Section number and Name	**Description of Change**	**Brief Rationale**
9.2.3 Follow-up of serious adverse events; 9.2.4 After the 30-day follow-up period; 9.2.5 Reporting procedures	The 'Actelion Global Drug Safety department' and 'Actelion' are updated as 'Sponsor'.	Updated reporting and follow-up procedures for serious adverse events (SAEs).as part of Actelion and Janssen integration.
9.2.5 Reporting procedures	Information about Sponsor's and investigator's responsibility in reporting all suspected unexpected serious adverse reactions (SUSARs) is updated.	Updated reporting procedures for SUSARs as part of Actelion and Janssen integration.
9.3.1 Reporting of pregnancy; 9.3.2 Follow-up of pregnancy	Information about reporting and follow-up procedures for pregnancy is updated.	To reflect the standard Janssen wording and include monitoring of pregnant partners of male patients per Janssen safety reporting procedures as part of the ongoing integration of Actelion into the Janssen ecosystem.
9.4 Product quality complaint handling	A new section on PQC handling and reporting is added.	PQC handling section added to comply with internal procedures due to Actelion and Janssen safety process integration.
9.5 Special reporting situations	A new section is included to define special reporting situations.	To be consistent with Janssen safety integration processes.
12.12 Reporting of study results and publication	Statement regarding Actelion's policy for study data disclosure is revised as: '**Janssen Pharmaceutical Companies (Actelion) will post results from Phase 1-4 clinical studies on external registries as required by law and from interventional studies in patients for marketed products**.'	To follow Janssen's policy on scientific publications.
Throughout the protocol	Minor corrections and editorial revisions.	To maintain consistency throughout and to improve clarity of the content.

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CEC	Clinical Event Committee
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CL	Confidence limit
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DAOH	Days alive and out of the hospital
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
FAS	Full Analysis Set
FC	Functional class
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction

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
LFT	Liver Function Test
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OL	Open-label
OLE	Open-label Extension Enrolled Set
PAD	Peripheral artery disease
PAH	Pulmonary arterial hypertension
PDE-5	Phosphodiesterase-5
PH	Pulmonary hypertension
PI	Principal Investigator
PQC	Product Quality Complaint
PTOP	Post-treatment observation period
PVD	Pulmonary Vascular Disease
RSI	Reference safety information
RVD	Right ventricular dysfunction
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SBP	Systolic blood pressure
SCL	Study Closure
SpO_2	Oxygen saturation
SI	International system of units
SIV	Site Initiation Visit
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
USA	United States of America
VHP	Voluntary Harmonization Procedure
VSFU	Vital Status Follow-Up
WHF	Worsening heart failure

PROTOCOL SYNOPSIS AC-055G203

TITLE	A long-term, multicenter, single-arm, open-label extension of the SERENADE study, to assess the safety and efficacy of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease
ACRONYM	SERENADE OL Macitentan in heart failure with pre**SER**ved ej**E**ction fractio**N** and pulmon**A**ry vascular **D**iseas**E** **O**pen **L**abel
OBJECTIVES	**Main objective(s)** To evaluate the long-term safety of macitentan 10 mg in subjects with heart failure due to preserved ejection fraction and pulmonary vascular disease. **Secondary objective(s)** To explore the long-term efficacy of macitentan 10 mg.
DESIGN	A multi-center, single-arm, open-label (OL) Phase 2b extension study. All subjects will receive the same study treatment.
PERIODS	**Pre-OL treatment period:** Starts with the signature of the Informed Consent Form (ICF) and ends with the administration of the first dose of OL study treatment. **Treatment period:** Starts with the administration of the first dose of OL study treatment and ends on the day of the last dose of OL study treatment. **Follow-up period:** Starts on the day after the last dose of OL study treatment and ends 30 days thereafter with the End-of-Study (EOS) Visit. The safety follow-up visit will be waived in case the subject moves to a continued access program and in that case EOT will be the last visit in the study.
PLANNED DURATION	SERENADE OL starts with the first act of recruitment (i.e., first ICF signed) and ends with the last visit of the last subject. SERENADE OL will continue at each site until all subjects have left the study, or until Actelion decides to stop the study (e.g., if the results of the main study show that the use of macitentan in this patient population is either not safe or not effective), whichever occurs first.

	Per request from VHP, the following applies for VHP countries: For each subject, the OL treatment duration will last up to 260 weeks (5 years) from his/her enrollment (Visit 1). The study may end earlier if all subjects have left the study, or if Actelion decides to stop the study (e.g., if the results of the main study show that the use of macitentan in this patient population is either not safe or not effective). Likewise, if during the course of the OL study, the Independent Data Monitoring Committee (IDMC) concludes that the use of macitentan in this patient population is either not safe or not effective, the main study (if still ongoing) and the OL study will be stopped.
SITE(S) / COUNTRY(IES)	Approximately 77 sites in 17 countries
SUBJECTS / GROUPS	Approximately 112 subjects in 1 group (Macitentan open-label)
INCLUSION CRITERIA	1. Signed and dated ICF. 2. Subject remained in the main study (SERENADE / AC-055G202) for: a. 52 weeks after randomization if entered this OL extension study prior to protocol Version 4 [see Section 4.1]. b. At least 24 weeks after randomization if entering this OL extension study under protocol Version 4 [see Section 4.1]. 3. A woman of childbearing potential [see definition in Section 4.4.1] is eligible only if the following applies: • Negative pre-treatment serum pregnancy test. • Agreement to undertake monthly pregnancy tests from the enrollment visit up to at least 30 days after study treatment discontinuation. • Agreement to use reliable contraception [Section 4.4.2] from at least 30 days prior to the enrollment visit up to at least 30 days after study treatment discontinuation.
EXCLUSION CRITERIA	1. Premature discontinuation of study treatment in the main study due to an adverse event related to: a. Edema or fluid retention b. Worsening of heart failure c. Liver aminotransferase elevation d. Study treatment, based on investigators' discretion

	2. Liver aminotransferase elevations, at the enrollment visit[1], fulfilling the following criteria: a. Alanine aminotransferase (ALT) / aspartate aminotransferase (AST) ≥ 8 × the upper limit of normal range (ULN) b. ALT/AST ≥ 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) c. ALT/AST ≥ 3 × ULN and associated increase in total bilirubin to ≥ 2 × ULN 3. Criteria modified per Amendment 4 3.1 Treatment with the following forbidden medications within 1 month prior to the enrollment visit: a. Treatments that may interfere with the assessment of efficacy (i.e., endothelin receptor antagonists, prostanoids, phosphodiesterase-5 inhibitors, guanylate cyclase stimulators) b. Strong cytochrome P-450 3A4 (CYP3A4) inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, or St. John's wort c. Strong CYP3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir or a moderate dual CYP3A4/CYP2C9 inhibitor (eg, fluconazole or amiodarone) or co-administration of a combination of moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (eg, miconazole, piperine), in the 1-month period prior to baseline. This will not necessarily apply to subjects who are already well-managed on such an ongoing combination. d. any other investigational treatment. 4. Pregnant, planning to be become pregnant or lactating. 5. 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.

[1] In case the central laboratory results at enrollment show ALT/AST elevations ≥ 3 × ULN, study treatment must not be initiated until the values return to pre-enrollment levels or within normal range. Please follow the instructions in Section 5.1.9.1.

	6. Known hypersensitivity to macitentan or drugs of the same class, or any of the study drug excipients (e.g., soy lecithin, lactose).
STUDY TREATMENTS	**Investigational treatment** Macitentan oral tablet, 10 mg once daily
ENDPOINTS	**Primary efficacy endpoint(s)** No primary efficacy endpoint has been defined for this study. **Exploratory efficacy endpoints** • Time to worsening heart failure event Time to first occurrence of a composite of heart failure (HF) death or HF hospitalization • Time to first occurrence of a composite of cardiovascular (CV) death or CV hospitalization • New York Heart Association class (improved/worsened/ stable) at each post-baseline assessment **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 adverse events (AEs) and serious adverse events 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 all assessed timepoints during the study • Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation • Change in laboratory parameters from baseline to all assessed timepoints during the study • Change from baseline in estimated glomerular filtration rate (eGFR) to all assessed timepoints during the study.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	The analyses will combine data from the main study with additional data from this open label extension to provide long-term follow-up data, in subjects who were exposed to macitentan in the double-blind phase of the main study and/or in SERENADE OL. Analyses will be conducted to assess the long-term safety and efficacy of macitentan

	in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease. The SERENADE OL study will contain analyses related to exploratory efficacy and safety endpoints. No formal hypothesis testing will be performed as all efficacy analyses are considered exploratory. Data will be summarized using descriptive statistics. In addition, plots of profiles over time will be displayed for continuous outcomes. Any p-values are presented for information only. No multiplicity adjustment will be made. Efficacy will be analyzed including data from both SERENADE and SERENADE OL and presented by randomized treatment group in the main study. Full details of the analyses will be described in the SAP. The Safety Set will be used for the analyses of the safety variables and includes all subjects who received at least one dose of open-label treatment in the study. The results will be presented overall and by previous double-blind treatment group in the main study. Baseline value will be the last non-missing assessment obtained prior to the start of study drug intake in SERENADE OL. Safety will also be evaluated on the Safety initiated Set including subjects who received macitentan treatment in the main study and/or macitentan treatment in SERENADE OL. Baseline will be the last non-missing value obtained prior to the start of macitentan intake in the main study or SERENADE OL, respectively. The Open-label Extension Enrolled Set (OLE) includes all subjects who enrolled into SERENADE OL. The OLE Set is used for the description of subject disposition in the OL extension, as well as the description of this study population at baseline.
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.

	A Steering Committee has contributed to the study design and will be consulted prior to and during the study for relevant medical issues and study publications. External to the study, 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 any macitentan study as per the ILSDRB charter.

PROTOCOL

1 BACKGROUND

1.1 Indication

Heart failure (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 HF 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; and c) evidence of abnormal left ventricular 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 HF with reduced ejection fraction [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, 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 A (ET_A) and endothelin B (ET_B) endothelin receptor antagonist (ERA), which has been approved for the treatment of pulmonary arterial hypertension (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

The rationale for SERENADE/AC-055G202, hereinafter referred to as the 'main study,' relies on the hypothesis that patients with HFpEF and pulmonary vascular disease may benefit from treatment with macitentan because of its mechanism of action. Pre-clinical data suggest that dual ET receptor blockade can directly improve cardiac remodeling, and especially decrease fibrosis, leading to an improvement of the filling capacity of the left ventricle. The subset of HFpEF patients with pulmonary vascular disease (PVD) with or without Right ventricular dysfunction (RVD) is most likely to benefit from treatment with an ERA. ERAs, including macitentan, demonstrated efficacy and are generally well tolerated in subjects with PAH with a varied degree of RVD. Furthermore, in a small, exploratory phase 2 study of macitentan in combined pre-and post-capillary pulmonary hypertension, AC-055G201/MELODY-1 [Vachiéry 2018], evaluation of pulmonary hemodynamics showed an increase in cardiac output that was not associated with elevated cardiac filling pressures. Furthermore, a 23% reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) compared to placebo was observed. Although the study was not powered to assess efficacy, the observed improvements suggest a potential benefit of macitentan in those subjects who are able to tolerate macitentan (i.e., who do not develop significant fluid retention). The aim of the main study is to confirm these exploratory findings, and to evaluate whether they translate into a clinically meaningful benefit.

The purpose of this open-label (OL) extension study is to gather additional longer-term safety and efficacy data with macitentan 10 mg in subjects with HFpEF and PVD beyond 24 weeks[2] of treatment in the double-blind SERENADE study (AC-055G202).

Furthermore, this OL extension study will give eligible subjects who have completed the main study an opportunity to continue or start receiving macitentan 10 mg.

1.4 Summary of known and potential risks and benefits

The SERENADE OL study will start while the main study (SERENADE / AC-055G202) is still ongoing, i.e., at the time of entry into the OL extension, the treatment allocation in the main study will still be blinded.

Previous studies with ERAs in HF have consistently shown increased incidences of early fluid retention events [Section 1.3]. To mitigate the risks associated with fluid retention events, the SERENADE study was designed to include a 4-week placebo run-in period to ensure the subjects' clinical stability, followed by a 5-week macitentan run-in period to identify those subjects who were unable to tolerate macitentan because of an increased susceptibility to developing macitentan-induced fluid retention events. To ensure that only subjects able to tolerate macitentan entered the double-blind treatment period, the SERENADE protocol pre-specified strict run-in failure criteria which, if met, required premature discontinuation of the subject from the study.

Although the results of the main study are not available at the time of entry into the OL extension, the risks of participating in the OL extension study are mitigated by the above-mentioned strict criteria for entering the double-blind period of the main study. In addition, a subject who experienced an adverse event (AE) leading to study treatment discontinuation related to edema/fluid retention, worsening heart failure (WHF), or liver aminotransferase elevations in the main study, will not be eligible for safety reasons.

To ensure the safety of subjects who have been on placebo in the main study, all subjects will return for a safety visit 1 week (±2 days) after the start of open-label study treatment.

It is the investigator's responsibility to monitor the risk-benefit 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' wellbeing.

[2] If subjects entered this OL extension study prior to protocol Version 4, then transition to this OL extension study was only allowed from 52 weeks post-randomization.

2 STUDY OBJECTIVES

2.1 Main objective

To describe the long-term safety of macitentan 10 mg in subjects with HFpEF and pulmonary vascular disease.

2.2 Secondary objective

To explore the long-term efficacy of macitentan 10 mg.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design and rationale

This is a multi-center, single-arm, OL Phase 2b extension study [Figure 1].

Subjects who remained in main study for at least 24 weeks[3] after randomization and who meet the eligibility criteria described in Sections 4.2 and 4.3 will be eligible to enter this OL study. Assuming a 20% discontinuation from the main study, approximately 112 subjects are expected to enter the OL study, which will be conducted at the sites participating in the main study (i.e., 77 sites in 17 countries).

3.1.1 Study periods

The SERENADE OL study comprises the following consecutive periods:

Pre-OL treatment period: Starts with the signature of the informed consent and ends with the administration of the first dose of OL study treatment.

Treatment period: Starts with the administration of the first dose of OL study treatment and ends on the day of the last dose of OL study treatment.

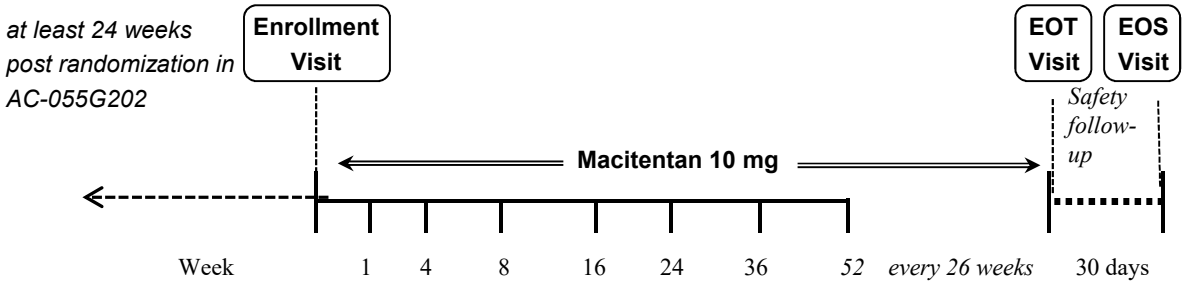
Follow-up period: Starts on the day after the last dose of OL study treatment and ends 30 days thereafter with the End-of-Study (EOS) Visit. The safety follow-up visit will be waived in case the subject moves to a continued access program and in that case EOT will be the last visit in the study.

The transition from the main study to SERENADE OL is described in Section 7.1.1. The visit schedule and protocol-mandated procedures are performed according to the table of assessments [Table 1] and are described in Section 7.

The overall study design is depicted in [Figure 1].

[3] If subjects entered this OL extension study prior to protocol Version 4, then transition to this OL extension study was only allowed from 52 weeks post randomization.

Figure 1 Study design



EOS = End-of-Study; EOT = End-of-Treatment

3.1.2 Study duration

SERENADE OL starts with the first act of recruitment (i.e., first Informed Consent Form [ICF] signed) and ends with the last visit of the last subject.

SERENADE OL will continue at each site until all subjects leave the study, or until Actelion decides to stop the study (e.g., if the results of the main study show that the use of macitentan in this patient population is either not safe or not effective), whichever occurs first.

Per request from VHP, the following applies for VHP countries: For each subject, the OL treatment duration will last up to 260 weeks (5 years) from his/her enrollment (Visit 1). The study may end earlier if all subjects have left the study, or if Actelion decides to stop the study (e.g., if the results of the main study show that the use of macitentan in this patient population is either not safe or not effective).

Study Closure (SCL) will be announced by the sponsor when all subjects have discontinued study treatment. For an individual subject, the study is completed with the EOS Visit; however, for subjects who have had their EOS visit more than 8 weeks prior to the SCL announcement, a vital status follow-up (VSFU) will be performed within 4 weeks after the SCL announcement to determine each subject's vital status at this time, unless already known (i.e., subject died, withdrew consent, or is lost to follow-up). This information will be collected in the CRF after the sponsor announces SCL.

The SCL will occur when the EOS Visit of the last subject and all VSFUs have been performed/attempted.[4]

[4] Apply lost to follow-up rules [Section 8.2] for attempts on VSFU

3.2 Study committees

The same committees as in the main study will be used:

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.

A Steering Committee has contributed to the study design and will be consulted prior to and during the study for relevant medical issues and study publications

External to the study, 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 any macitentan study as per the ILSDRB charter.

4 SUBJECT POPULATION

4.1 Subject population description and rationale

The study will enroll male and female subjects with an established diagnosis of HFpEF and pulmonary vascular disease with or without overt RVD. As this is an OL extension of study AC-055G202 (SERENADE), only subjects who were randomized in the main study, remained in the main study for at least 24 weeks[5] after randomization, and who meet the criteria described in Sections 4.2 and 4.3, are eligible for participation.

Remaining in the main study is defined as follows:

- Subjects who completed the treatment period (Core and Extension phase) as per main study protocol and had their End-of Treatment (EOT) Visit at Week 52 (–8 days) if entering this study prior to SERENADE OL protocol Version 4.
- Subjects who completed the Core treatment period as per main study protocol and had their EOT Visit at Week 24 (–8 days) or later if entering this study under SERENADE OL protocol Version 4.

[5] If subjects entered this OL extension study prior to global protocol version 4 then transition to this OL extension study was only allowed following 52 weeks post randomization.

- Subjects who prematurely discontinued study treatment but participated in the Post-treatment observation period (PTOP) until Week 52 / PTOP4 (–14 days). Only applicable for subjects who have transitioned to the OL extension study prior to SERENADE OL protocol Version 4.
- Subjects who prematurely discontinued study treatment but participated in the PTOP until at least Week 24 / PTOP2 (±14 days) if entering under SERENADE OL protocol Version 4.

4.2 Inclusion criteria

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

1. Signed and dated informed consent form.
2. Subject remained in the main study (SERENADE/AC-055G202) for:
   a. 52 weeks after randomization if entered this OL extension study prior to protocol Version 4 [see Section 4.1].
   b. At least 24 weeks after randomization if entering this OL extension study under protocol Version 4 [see Section 4.1].
3. A woman of childbearing potential [see definition in Section 4.4.1] is eligible only if all of the following apply:
   - Negative pre-treatment serum pregnancy test.
   - Agreement to undertake monthly pregnancy tests from the enrollment visit up to at least 30 days after study treatment discontinuation.
   - Agreement to use reliable contraception [Section 4.4.2] from at least 30 days prior to the enrollment visit up to at least 30 days after study treatment discontinuation.

4.3 Exclusion criteria

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

1. Premature discontinuation of study treatment in the main study due to an adverse event related to:
   a. Edema or fluid retention
   b. Worsening of HF
   c. Liver aminotransferase elevations.
   d. Study treatment, based on investigators' discretion

2. Liver aminotransferase elevations, at the enrollment visit[6], fulfilling the following criteria:
   a. Alanine amino transferase (ALT) / aspartate aminotransferase (AST) ≥ 8 × the upper limit of normal (ULN)
   b. ALT/AST ≥ 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)
   c. ALT/AST ≥ 3 × ULN and associated increase in total bilirubin to ≥ 2 × ULN.
3. Criteria modified per Amendment 4
   3.1Treatment with the following forbidden medications within 1 month prior to the enrollment visit:
   a. Treatments that may interfere with the assessment of efficacy (i.e., ERAs, prostanoids, phosphodiesterase-5 (PDE-5) inhibitors, guanylate cyclase stimulators)
   b. Strong cytochrome P450 3A4 (CYP3A4) inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, or St. John's wort
   c. Strong CYP3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir or a moderate dual CYP3A4/CYP2C9 inhibitor (e.g. fluconazole or amiodarone) or co-administration of a combination of moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (eg, miconazole, piperine), in the 1-month period prior to baseline. This will not necessarily apply to subjects who are already well-managed on such an ongoing combination.
   d. any other investigational treatment.
4. Pregnant, planning to be become pregnant or lactating.
5. 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.
6. Known hypersensitivity to macitentan or drugs of the same class, or any of the study drug excipients (e.g., soy lecithin, lactose).

[6] If there is a known AST/ALT elevation, the site should not initiate OL treatment. In case the central laboratory results from enrollment visit show ALT/AST elevations ≥ 3 × ULN, study treatment must be interrupted until the values return to pre-enrollment levels or within normal range. Please follow the instructions in Section 5.1.9.1.

4.4 Criteria for women of childbearing potential

4.4.1 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]),
- 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).

4.4.2 Acceptable methods of contraception

Women of childbearing potential [see definition in Section 4.4.1] must use acceptable birth control from enrollment to at least 30 days after study treatment discontinuation. Reliable contraception must be used for at least 30 days prior to the enrollment visit.

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.

4.4.2.1 Countries where macitentan is approved

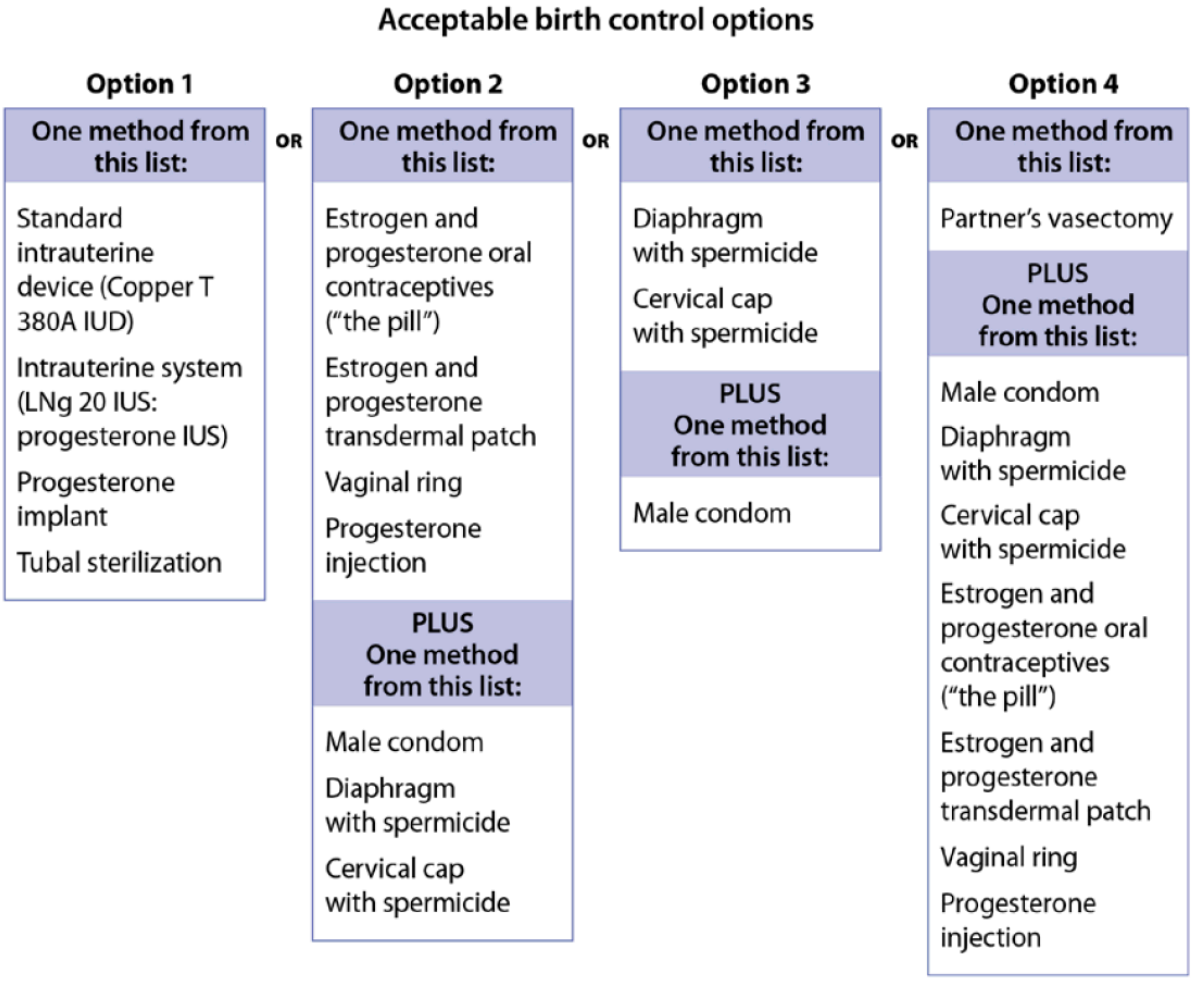
In countries where macitentan is approved, the macitentan label can be followed with respect to acceptable methods of contraception. It must be ensured that a female counselor is available to discuss this topic, if requested.

4.4.2.2 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



Per request from VHP, the following applies for VHP countries:

The sole use of double-barrier methods (Option 3) can only be accepted when the use of highly effective measures is medically contraindicated. The contraindication must be documented in the patient chart.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment: Description and rationale

The investigational treatment is macitentan (ACT-064992, Opsumit®), tested at the same dose (i.e., 10 mg) as in the main study.

Macitentan is provided as film-coated tablets debossed with '10' on both sides. One tablet must be taken orally once a day.

5.1.2 Study Treatment Administration

The first intake of study treatment will take place at site, during Visit 1 (enrollment). 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 2, where the study treatment is taken from the bottle dispensed at Visit 1).

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 two doses to make up for a missed dose.

5.1.3 Treatment assignment

After having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the Interactive Response Technology (IRT) system at the enrollment visit to enroll the subject. All subjects will retain the subject number they were assigned in the main study. The IRT assigns the study treatment bottle number(s).

5.1.4 Blinding

Not applicable, as this is an OL extension study.

The treatment assignment in the main study will remain blinded until the time of unblinding for final data analysis of the main study. Subjects will therefore enter the OL extension without knowledge of their treatment assignment in the main study.

5.1.5 Study treatment supply

Manufacturing, 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.

5.1.5.1 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.

5.1.5.2 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.

5.1.5.3 Study treatment dispensing

The subjects will receive sufficient study treatment (i.e., up to 6 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 doesn't 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.

5.1.5.4 Study treatment return and destruction

Study treatment must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment and study treatment returned by the subject must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study treatment or used returned study treatment for destruction will be documented on the intervention return form. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the intervention return form.

5.1.6 Study treatment accountability and compliance with study treatment

5.1.6.1 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 Clinical Research Associate (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.

5.1.6.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated by site personnel at each study treatment dispensing visit and EOT using the below formula and entered in the CRF:

Compliance = [(number of tablets dispensed – number of tablets returned) / Total number of tablets that should have been taken between 2 regular study treatment dispensing visits*] × 100

*The number of tablets that should have been taken is derived from the number of days between the corresponding regular visits.

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.

5.1.7 Study treatment dose adjustments and interruptions

Study dosage 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 5.1.9.

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 5.1.8].

Study treatment interruptions must be recorded in the CRF.

5.1.8 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., AE or lack of efficacy), the investigator (e.g., due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy), or Actelion (e.g., study termination) must be documented in the CRF.

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 5.1.9.

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

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered withdrawn from the study. Subjects who die or are lost to follow-up are also considered 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.

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

5.1.9.1 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.

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:

- ALT/AST ≥ 8 × ULN
- ALT/AST ≥ 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 medications or other substances) should be considered and ruled out by performing the appropriate tests.

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

5.1.9.2 Hemoglobin abnormalities

If there is a decrease in hemoglobin from baseline[7] of > 20 g/L during the first 6 months of OL study treatment (i.e., up to Visit 6 / Week 24), a re-test must be performed within

[7] Baseline hemoglobin refers to the hemoglobin value obtained at Visit 1 (enrollment visit).

10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

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

If hemoglobin remains > 20 g/L below baseline value at subsequent visits, or if hemoglobin decreases > 20g/L below baseline value after Visit 6 / Week 24, 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. 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. Interruption of study medication must not last longer than 4 consecutive weeks; longer interruption must lead to permanent discontinuation of study drug.

5.1.9.3 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 as detailed in Section 5.2.4 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.

5.1.9.4 Pregnancy

If a female subject becomes pregnant while on study treatment, study treatment must be permanently discontinued immediately, and a Pregnancy Notification Form must be completed [see Section 9.3.1].

5.1.10 Study treatment overdose and treatment

For this study, any dose of study medication higher than the planned total daily dose in a single day will be considered an overdose.

In the event of an overdose, standard supportive measures must be taken, as required.

5.2 Previous and concomitant medications

5.2.1 Definitions

A previous medication is any treatment for which the end date is prior to the enrollment visit.

A medication that is study-concomitant is any treatment that is ongoing or initiated after the enrollment visit or initiated up to 30 days after study treatment discontinuation.

5.2.2 Reporting of previous/concomitant medications in the CRF

The use of all study-concomitant medications (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the CRF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency and indication will be recorded in the CRF.

5.2.3 Allowed concomitant therapy

- Standard oral therapy for HF, including beta-blockers, ACE inhibitors or ARBs, and diuretics will be continued and adjusted as medically indicated.
- For subjects with a systolic blood pressure (SBP) > 150 mmHg, treatment with antihypertensives according to local guidelines [ESC Guidelines 2013, James 2014] to achieve their target blood pressure (BP) is recommended.

5.2.4 Forbidden concomitant therapy

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

- Endothelin receptor antagonists (other than macitentan 10 mg)
- Strong CYP3A4 inducers (eg, carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifabutin, rifapentin, St. John's wort).
- 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 [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.

- Any other investigational drug.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint(s)

No primary efficacy endpoint has been defined for this study.

6.1.2 Exploratory efficacy endpoints

- Time to WHF event
- Time to first occurrence of a composite of HF death[8] or HF hospitalization[8]
- Time to first occurrence of a composite of cardiovascular (CV) death[8] or CV hospitalization[8]
- New York Heart Association functional class (NYHA FC) (improved/worsened/stable) at each post-baseline assessment

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 serious AEs (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 all assessed timepoints during the study
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation
- Change in laboratory parameters from baseline to all assessed timepoints during the study
- Change from baseline in estimated glomerular filtration rate (eGFR) to all assessed timepoints during the study

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 General information

The study visits are listed in Table 1. For all visits, the subjects must be seen on the designated day with the allowed visit window. A follow-up safety visit must be performed

[8] See definition of HF death and CV death in Appendix 4; See definition of HF hospitalization and CV hospitalization in Appendix 5.

30 + 5 days after intake of the last dose of OL study treatment. If it is not possible to complete all assessments on the same day, a visit may extend over more than 1 day within the allowed time window. The safety follow-up visit will be waived in case the subject moves to a continued access program and in that case EOT will be the last visit in the study. (see Section 8.4).

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 making the decision to stop study treatment.

7.1.1 Transition to SERENADE OL

A subject may transition to the OL extension study after having remained in the main study for at least 24 weeks[9] after randomization.

The enrollment visit will be combined with the EOT Visit of the main study. If combination of the visits is not possible, the OL enrollment visit may be done separately up to 30 days after intake of the last dose of study treatment. This transition period may be extended if full approval of the SERENADE OL protocol is not obtained on time. For subjects who prematurely discontinued study treatment and do not meet any of the exclusion criteria listed in Section 4.3, the enrollment visit will be combined with the corresponding PTOP or EOS visit[9].

7.1.2 Informed consent

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 this SERENADE OL study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure. Informed consent to participate in SERENADE OL may be obtained before or after completion of the main study. The time between signature of the ICF and the SERENADE OL enrollment visit should not exceed 1 month.

The pre-OL treatment period starts with the signature of the informed consent. The date on which the first SERENADE OL protocol-mandated assessment is performed corresponds to the date of the enrollment visit.

Subjects will be consented to SERENADE OL Version 4 at the next regular visit.

[9] If subjects entered this OL extension study prior to protocol version 4, then transition to this OL extension study was only allowed following 52 weeks post randomization or post PTOP4 visit at 52 weeks in case of premature discontinuation from double-blind treatment.

7.1.3 Unscheduled visits

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

Table 1 Visit and assessment schedule

PERIODS	**Name**	**OPEN LABEL TREATMENT**								**FOLLOW-UP**
VISITS[1]	**Number**	**1**	**2**	**3**	**4**	**5**	**6, 7, 8,**	**9-x[5]**		
	Name	**Enrollment[3]**	**Week 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24, 36, 52**	**Week 78, 104, 130**	**EOT[5]**	**EOS[4]**
	Time	**SD 1**	**SD 7 (± 2)**	**SD 28 (± 4 d)**	**SD 56 (± 7 d)**	**SD 112 (± 14 d)**	**SDs 168, 252, 364 (±14 d)**	**Every 26 (±14 d)**	**Within 7 d after last dose**	**30 (+ 5 d) days after last dose**
Informed consent[2]		X								
Eligibility		X								
Concomitant therapy		X#	X	X	X	X	X	X	X	X
Physical examination		X#	X	X	X	X	X	X	X	X
Vital signs (BP, HR)		X#	X	X	X	X	X	X	X	X
Body weight		X#	X	X	X	X	X	X	X	X
Home body weight monitoring		← Weekly →								
NYHA FC		X#	X	X	X	X	X	X	X	X
WHF		X#	X	X	X	X	X	X	X	X
Hematology/Clinical chemistry/ serum pregnancy test*[6,7]		X#		X	X[8]	X[8]	X[8]	X[8]	X	X
Urine pregnancy test[9]					← Monthly in-between visits →					
Study treatment dispensing		X		X	X	X	X	X		
SAEs/AEs[10]		X	X	X	X	X	X	X	X	X

*Transferred electronically by an external service provider

If the EOT (or corresponding PTOP/EOS) Visit of the main study and the enrollment visit of the OL extension are combined, the results of these assessments and corresponding actions, as applicable, need to be reported in the CRFs of the main study only.

[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] Informed consent may be signed prior to Visit 1 or at Visit 1.

[3] During enrollment, if it is not possible to perform all assessments in one day, the procedures can be done any time prior to Visit 2.

[4] For subjects who had their EOS Visit more than 8 weeks prior to study closure (SCL) announcement, a vital status follow-up visit (VSFU) will be performed by the site within 4 weeks after the SCL announcement. VSFU does NOT need to be performed if the subject's vital status is known (i.e., loss to follow-up, death, withdrawal of consent) In addition to the VSFU at the time of SCL, the sponsor may request this information be obtained at any time during the study.

[5] **Per request from VHP, the following applies for VHP countries:** Visits 9 through 15 only, occurring at weeks 78, 104, 130, 156, 182, 208, 234, respectively. EOT Visit will be at Week 260 (±14 days). In case of premature discontinuation, the EOT Visit must be within 7 days after the last dose.

[6] Sent to the central laboratory.

[7] For women of childbearing potential only.

[8] Monthly AST/ALT monitoring is recommended. It is at the investigator's discretion to decide (taking into account the subject's medical history and AEs) if those monthly tests are required/justified. Local laboratory may be used. **Per request from VHP, the following applies for VHP countries:** monthly AST/ALT monitoring is **required**. Local laboratory may be used for monthly AST/ALT monitoring in between visits.

[9] For women of childbearing potential only: Urine pregnancy test will be performed by the subject on a monthly basis, in-between visits. The site will follow-up on the results with a telephone call.

[10] All AEs and SAEs that occur after intake of the first dose of OL study treatment and up to 30 days after study treatment discontinuation must be reported [see also Section 9].

AE = adverse event; BP = blood pressure; SD = Study Day; d = days; EOS = End-of-Study; EOT = End-of-Treatment; FC = functional class; HR = heart rate; NYHA = New York Heart Association; SAE = serious adverse event; SCL= study closure; VHP = voluntary harmonization procedure; VSFU = vital status follow-up visit; W = Week; w = weeks; WHF = worsening heart failure; PTOP = post-treatment observation period.

7.2 Study assessments

The study assessments are listed in Table 1. 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 is recommended:

- Physical examination (including assessment of AEs/SAEs), vital signs, NYHA FC, body weight, concomitant therapy, WHF)
- Blood sampling

If the Principal Investigator (PI) delegates any study procedure/assessment for a subject, e.g., 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 enrollment of the first subject. Calibration certificates of other equipment must be available as per local requirements.

- Temperature measurement devices for study treatment storage area
- Body-weight scale

7.2.1 Demographics / baseline characteristics

Demographic data (sex, race and ethnicity), baseline disease characteristics and medical history recorded in the database of the main study will be used.

Where possible, diagnoses and not symptoms will be recorded.

For subjects who were not eligible to enter SERENADE OL, the following data will be recorded in the CRF if available:

- Date/Time of ICF signature
- Reason for non-eligibility and associated assessments, if applicable.

7.2.2 Efficacy assessments

7.2.2.1 Assessment of WHF event

Occurrence of a WHF event will be assessed by the investigator using the 2015 American College of Cardiology / American Heart Association definition [ACC/AHA2015, Appendix 3].

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]

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]

*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 2 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
	• Non-invasive 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.
		  ◦ *Vasoactive therapy may include an* i.v. *inotrope, vasodilator, or vasopressor.*
		• Mechanical or surgical intervention, including:
		  ◦ *Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart).*
		  ◦ *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.

7.2.2.2 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.

7.2.3 Safety assessments

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

7.2.3.1 Vital Status

For subjects who had their EOS Visit more than 8 weeks prior to SCL announcement, a VSFU will be performed by the site within 4 weeks after the SCL announcement to determine each subject's vital status (alive, dead, or unknown) at this time.

In addition to the VSFU at the time of SCL, the sponsor may request that this information be obtained at any time during the study.

This VSFU will be performed by the investigational site via a contact with the subject or legal representatives/caregivers (phone call or any other means allowed per local regulations, e.g., access to public registries).

The outcome of the VSFU is reported in the CRF.

7.2.3.2 Physical examination

Physical examination 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 the investigator's discretion.

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

Results of all physical examinations must be documented in the patient's chart at the study site. Significant physical examination findings made after enrollment, 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 diastolic BP (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

Body weight will be measured at the site at all visits. It is recommended to always weigh individual subjects 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 weekly basis from enrollment until Week 16, 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.

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

Hematology and chemistry tests will be performed at the visits indicated in Table 1.

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.

Monthly AST/ALT monitoring is recommended. It is at the investigator's discretion to decide (taking into account the subject's medical history and AEs) if those monthly tests are required/justified. Local laboratories may be used.

If monthly AST/ALT monitoring in between visits is performed, a local laboratory can be used. The results from the local AST/ALT tests that are within normal range do not need to be reported in the CRF. If the local laboratory results show an increase in AST/ALT

≥ 3 × ULN, the results must be reported in the CRF, the subject must return to the site and the AST/ALT re-test must be performed centrally.

Per request from VHP, monthly AST/ALT monitoring is required in all VHP countries. Local laboratories may be used for monthly AST/ALT monitoring in between visits. The results from the local AST/ALT tests that are within normal range do not need to be reported in the CRF. If the local laboratory results show an increase in AST/ALT ≥ 3 × ULN, the results must be reported in the CRF, the subject must return to the site and the AST/ALT re-test must be performed centrally.

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. Any clinically relevant laboratory abnormalities detected after administration of the first dose of OL study treatment 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

The amount of blood collected from an individual subject is approximately 10 mL at each visit which only collects hematology/clinical chemistry, including pregnancy test, if applicable. For details, please refer to the laboratory manual.

Hematology

- Hemoglobin (International system of units [SI]: 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)
- BUN (SI unit: mmol/L; Conventional unit: mg/dL)
- Uric acid (SI unit: µmol/L; Conventional unit: mg/dL)
- Sodium, potassium, chloride, calcium, magnesium (mmol/L)
- Total protein, albumin (SI unit: g/L; Conventional unit: g/L)
- Albumin / Globulins ratio
- eGFR (mL/min/1.73m^2), using the MDRD formula

Pregnancy test

Women of childbearing potential must have monthly pregnancy tests up to EOS.

At regular, scheduled visits, a serum pregnancy test will be performed [Table 1]. After Week 8, when the interval between visits exceeds 1 month, women of childbearing potential must perform urine pregnancy tests at home in between visits on a monthly basis in addition to the serum pregnancy tests 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.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

A subject who completes the safety follow-up period and EOS Visit is considered to have completed the study as per protocol. The safety follow-up visit will be waived in case the subject moves to a continued access program and in that case EOT will be the last visit in the study.

The VSFU will be collected in the CRF and is performed after study completion.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study (including VSFU) 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 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 wellbeing 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 Independent Ethics Committees (IECs) / Institutional Review Boards

(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 and Steering Committee.

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.

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of macitentan becomes available during the study or program.

At the end of their participation in the study, subjects who have completed the study and are benefiting from the study treatment, as determined by their investigator, will be able to receive continued access via an another open-label extension study or via post-study independent requests from their investigators.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse events

9.1.1 Definition of adverse events

An AE is any adverse change from the subject's baseline condition[10], 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, whether or not it is 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 of the study treatment and study treatment errors will be reported as an AE when associated with signs or symptoms.

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.

The three categories of intensity are defined as follows:

[10] Subject's condition prior to initiating the OL study treatment.

- **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 OL study treatment and reported as either related or not related. 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 administration of the first dose of OL study treatment and up to 30 days after OL study treatment discontinuation must be recorded on specific AE pages of the CRF. If the intensity of such an AE worsens, only the worst intensity needs to be reported on the AE form of the CRF.

Adverse events occurring prior to the administration of the first dose of OL study treatment are to be reported in the main study.

Ongoing AEs/SAEs:

AEs/SAEs that started during the main study and are still ongoing at the time of the first dose of OL study treatment will also be reported in the CRF of the SERENADE OL study.

If a non-serious, ongoing AE becomes serious during SERENADE OL, a new SAE must be reported in the SERENADE OL CRF. If a serious, ongoing AE becomes non-serious in SERENADE OL, no change is required to be reported.

If the intensity of an ongoing AE/SAE worsens during SERENADE OL, a new AE/SAE must be reported in the SERENADE OL CRF. Lessening of intensity of an ongoing AE/SAE during SERENADE OL does not need to be reported.

9.1.5 Follow-up of adverse events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or product quality complaint (PQC) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs still ongoing more than 30 days after OL 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 / telephone call 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
- Is a suspected transmission of any infectious agent via a medicinal product
- 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 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 as well as PQCs, occurring after administration of the first dose of OL study treatment and up to 30 days after OL 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.

For reporting of SAEs that are ongoing from the main study, please refer to Section 9.1.4.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship either to 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 / telephone call must be reported to Sponsor, 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 Sponsor 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 procedures

All SAEs must be reported by the investigator to Sponsor 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 Sponsor (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. Sponsor 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 the Sponsor in the reference safety information (RSI) section provided in the most recent version of the IB.

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate Pregnancy Notification Form. Any subject who becomes pregnant during the study must discontinue further study treatment (see Section 5.1.9.4).

9.3.2 Follow-up of pregnancy

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported on a SAE form as described in Section 9.2.5.

9.4 Product quality complaints handling

9.4.1 Definition

Product quality complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

9.4.2 Procedures

All initial PQCs must be reported to the Sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the Sponsor.

9.5 Special reporting situations

Safety events of interest on a sponsor study treatment in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study treatment
- Unexpected therapeutic or clinical benefit from use of a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a sponsor medicinal product (with or without patient exposure to the sponsor medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding.

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

9.6 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, 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 3.2]. Actelion may request additional 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 Contract Research Organizations (CROs) supervised by Actelion.

The analyses will combine data from the main study with additional data from this open label extension to provide long-term follow-up data, in subjects who were exposed to macitentan in the double-blind phase of the main study and/or in SERENADE OL. Analyses will be conducted to assess the long-term safety and efficacy of macitentan in subjects with HFpEF and pulmonary vascular disease.

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

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects randomized in the main double-blind study regardless of enrollment to SERENADE OL. Following the intent-to-treat principle, subjects are evaluated according to the study treatment they have been assigned to at randomization (which may be different from the study treatment they have received). The analyses of long-term efficacy may be further explored based on select cohorts within this analysis set. Full details will be described in the SAP.

10.1.2 Per-protocol Analysis Set

No Per-protocol analysis set is defined for SERENADE OL.

10.1.3 Safety Set

The Safety Set for SERENADE OL study includes all subjects who received at least one dose of OL treatment in the study.

10.1.4 Safety Initiated Set

All subjects who received any macitentan treatment in the main study and/or macitentan treatment in SERENADE OL. The main purpose of this cohort is to assess adverse events during treatment with macitentan.

10.1.5 Open-label Extension Enrolled Set

The Open-label Extension Enrolled (OLE) Set includes all subjects who enrolled into SERENADE OL.

10.1.6 Usage of the analysis sets

The FAS is used for the basis of the analysis of the exploratory efficacy variables [see Section 10.1.1].

The Safety Set is used for the analyses of the safety and efficacy variables in the OL study. The results will be presented overall and by previous double-blind treatment group in the main study. Baseline value will be the last non-missing assessment obtained prior to the start of study drug intake in SERENADE OL (OL Baseline). The main purpose of these analyses is to assess long-term safety and efficacy during OL study treatment regardless of randomized treatment in the main study.

The Safety Initiated Set is used for the analyses of adverse events and other select safety variables during treatment with macitentan. Baseline will be the last non-missing value obtained prior to the start of macitentan intake in the main study or SERENADE OL, respectively.

The OLE Set is used for the description of subject disposition in SERENADE OL as well as the description of this study population at baseline. Baseline for this will be the last non-missing assessment obtained prior to the start of study drug intake in SERENADE OL. Unless specified otherwise, individual listings are prepared on the OLE Set including any sub-study data (6MWD and Borg Dyspnea Index).

10.2 Variables

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

10.2.1 Primary efficacy variable(s)

There are no primary or secondary efficacy variables defined for SERENADE OL.

10.2.2 Exploratory efficacy variables

This section contains definitions of the variables related to the exploratory efficacy endpoints outlined in Section 6.1.2.

10.2.2.1 Time to first occurrence of WHF event

The time to first occurrence of WHF event.

All WHF events occurring until EOS are considered, irrespective of subjects' compliance to assigned therapies.

Subjects without any WHF event up to EOS are right-censored at their time of EOS.

Time to first occurrence of WHF event is expressed in days and calculated as the onset date of the first WHF event minus reference date plus 1 or, for censored subjects, as EOS date minus reference date plus 1. Where the analysis includes data combined with the main study the reference is the date of randomization, otherwise the reference is the date of enrollment in SERENADE OL.

10.2.2.2 Time to first occurrence of a composite of HF death or HF hospitalization

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 EOS are considered, irrespective of subjects' compliance to assigned therapies.

Subjects still alive at EOS and without any HF hospitalizations up to EOS are right-censored at their time of 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 reference date plus 1 or, for censored subjects, as EOS date minus reference date plus 1, where the reference date is applied as defined in Section 10.2.2.1.

10.2.2.3 Time to first occurrence of a composite of CV death or CV hospitalization

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 EOS are considered, irrespective of subjects' compliance to assigned therapies.

Subjects still alive at EOS and without any CV hospitalizations up to EOS are right-censored at their time of 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 reference date plus 1 or, for censored subjects, as EOS date minus reference date plus 1, where the reference date is applied as defined in Section 10.2.2.1.

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

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

An improvement corresponds to a decrease in NYHA FC by at least one level, whereas a worsening corresponds to an increase in NYHA FC by at least one level. Subjects remaining in the same NYHA FC 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 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 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 all assessed timepoints during the study
- Treatment-emergent marked laboratory abnormalities up all assessed timepoints during the study
- Change in laboratory parameters from baseline to all assessed timepoints during the study
- Change from baseline in eGFR up to all assessed timepoints during the study

10.2.4 Other variables

10.2.4.1 Exposure to study drug

The duration of exposure is defined as the time elapsing between study drug initiation and discontinuation, inclusive. This will be determined for exposure to macitentan in SERENADE OL and for exposure to macitentan for combined main study and SERENADE OL periods.

10.2.4.2 Discontinuation of SERENADE OL

The reasons leading to premature discontinuation of SERENADE OL study treatment and withdrawal from SERENADE OL study will be described.

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

This SERENADE OL study will contain analyses related to exploratory efficacy and safety endpoints. No formal hypothesis testing will be performed as all efficacy analyses are considered exploratory. As such, all confidence intervals (CIs) will be presented as 2-sided 90% CIs which is consistent with the main study where the sample size was based on alpha

= 0.1. Data will be summarized using descriptive statistics. In addition, plots of profiles over time will be displayed for continuous outcomes. Any p-values are presented for information only. No multiplicity adjustment will be made.

Efficacy will be analyzed (including data from SERENADE OL) on the FAS by randomized treatment group in main study. It is planned that the baseline for efficacy analysis will be the same as described for the main study Clinical Study Report (CSR).

Safety will be similarly analyzed using the Safety Set.

10.3.2 Analysis of the primary efficacy variable(s)

Not applicable.

10.3.3 Analysis of exploratory efficacy variable(s)

10.3.3.1 Time to event

The analyses of time-to-event variables [Sections 10.2.2.1, , 10.2.2.2, and 10.2.2.3] will be conducted using Kaplan-Meier estimates of events over time including graphical representation.

Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at relevant timepoints 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 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 timepoint.

Further details for the time-to-event variables will be described in the SAP.

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

The proportion (with 90% confidence limits [CLs]) of subjects having improved, having worsened or being stable at each post baseline visit will be summarized overall and by double-blind treatment group and may also presented as plots over time.

Handling of missing values will be detailed in the SAP.

10.3.4 Sub-group analyses

None planned.

10.3.5 Analysis of the safety variable(s)

All safety endpoints will be analyzed on the Safety Set and Safety Initiated Set as described in Section 10.1.6. Analyses on the safety set will be summarized by double-blind treatment group received in the main study.

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 summarized by:

- System Organ Class and Preferred Term within System Organ Class, in descending order of incidence
- Preferred Term, in descending order of incidence

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

The number and frequency of all-cause hospital admissions will be summarized.

10.3.5.3 Adverse events

All AEs will be coded using the latest available version of the MedDRA dictionary.

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/ with at least on AE with fatal outcome, will be tabulated by:

- System Organ Class and Preferred Term within System Organ Class, in descending order of incidence;
- Preferred Term, in descending order of incidence.

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 SAE, for all AEs leading to premature discontinuation of study treatment, and for all AEs with fatal outcome.

10.3.5.4 Adjusted incidence rates

In order to account for differences in the duration of exposure of study treatment among the subjects, incidence rates of AEs, SAEs, AEs leading to discontinuation, deaths, and hospitalizations will be presented as adjusted for patient-years exposure.

Methods for adjustment will be detailed in the SAP.

10.3.5.5 Vital signs and body weight

Descriptive summary statistics by visit will be provided for observed values and absolute changes from baseline in SBP, DBP, heart rate, and body weight.

10.3.5.6 Laboratory variables

Descriptive summary statistics by visit will be provided for observed values and absolute changes from baseline for laboratory variables. Data will be displayed in SI units as provided by the central laboratory.

Marked laboratory abnormalities will be summarized for each laboratory variable providing their counts and percentages of subjects with at least one treatment-emergent marked laboratory abnormality for each parameter for which the marked laboratory abnormality is defined.

All hematology and chemistry parameters provided by the central and local laboratory, will be displayed in subject listings in original and SI units, including those from unscheduled visits. Treatment-emergent marked abnormalities are flagged.

10.3.5.7 Glomerular Filtration Rate

Descriptive summary statistics by visit will be provided for observed values and absolute changes from baseline in GFR.

10.3.6 Analysis of other variables

Demographics and baseline characteristics, exposure to macitentan and subject disposition will be summarized overall and by treatment group in the main study. Sub-study (6MWD and Borg Dyspnea Index) data will be listed.

10.4 Interim analyses

No interim analyses are planned for the study.

Periodic review of the efficacy data in parallel to the safety data will be performed, allowing an assessment of risk/benefit by the IDMC [see Section 3.2]. An independent statistical analysis center (Frontier Science and Technology Research Foundation), involved in the main study but not otherwise involved in the design, conduct and analysis of the study, will prepare reports for review by the IDMC (for IDMC review meetings during the course of the trial) in accordance with the charter. There is no limit to the number of reviews meetings or reports, which have the aim of guaranteeing the safety of the subjects.

10.5 Sample size

The sample size for the SERENADE OL is expected to be approximately 112 subjects assuming 140 subjects randomized in the main study with a study discontinuation rate of 20% in the double-blind period of the main study.

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, 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 (refer to US 21 Code of Federal Regulations [CFR] Part 11).

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-specific 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 timepoint during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion 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.

As NT-ProBNP and MR-proANP are potentially unblinding variables, appropriate data processes will be implemented to ensure the blind is preserved and integrity of the main study maintained. Therefore, individual subject NT-proBNP and MR-proANP central laboratory data for subjects from whom NT-proBNP and MR-proANP samples were collected for SERENADE OL will not be shared with the site staff and the Sponsor's study team until closure of the main study.

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 Quality System 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

Only patients able to give their informed consent can be included in this study. 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. 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). This must be demonstrated by means of a personally signed and dated informed consent document indicating that the subject has been informed of and understood all pertinent aspects of the study.

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

Site personnel (according to local regulation) authorized to participate in the consent process and/or to obtain consent from the subject 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 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; 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.

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 Indemnification, compensation and refund of expenses 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 indemnification 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 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: the Investigator Site File (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 enrolling 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 Global Quality Management representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Actelion's requirements (e.g., standard operating procedures [SOPs]) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

The investigator and 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.

Janssen Pharmaceutical Companies (Actelion) will post results from Phase 1–4 clinical studies on external registries, as required by law and from interventional studies in patients for marketed products. 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.

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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	> 0.55 For Females > 0.60 For males	> 0.65	
Platelet count ($\times 10^9$ /L)	< 75	< 50	> 600	> 999	
Leucocytes ($\times 10^9$ /L)	< 3.0	< 2.0	> 20.0	> 100.0	
Neutrophils ($\times 10^9$/L)	< 1.5	< 1.0	NA	NA	
Eosinophils			> 5.0 × 10^9 or > 5%	NA	
Lymphocyte ($\times 10^9$/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	
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

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.

Total bilirubin flag alert value - all visits: Please refer to the study protocol for action regarding study medication (i.e., interruption or permanent discontinuation) in case of:

- Total bilirubin ≥ 2 ×ULN (In combination with ALT and/or AST ≥ 3 × ULN, study treatment must be stopped)

- **Interruption or permanent discontinuation of study medication - All visits except EOT and EOS:** Please refer to the study protocol for action regarding study medication (i.e., interruption or permanent discontinuation) [see Section 5.1.9] in case of the following laboratory abnormalities:

  - 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 test alert value - all visits except EOS:** Please refer to the study protocol for action regarding study medication (i.e., study treatment interruption or permanent discontinuation)

  - AST ≥ 3 × ULN
  - ALT ≥ 3 × ULN
  - Hemoglobin > 20 g/L decrease from baseline
  - Hemoglobin < 80 g/L
  - Hemoglobin > 50 g/L decrease from baseline

Appendix 3 Worsening Heart Failure Event definitions [ACC/AHA2015]

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” should 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; S3 = third heart sound; TVI = time velocity integral.

Appendix 4 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/AHA2015]

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 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 implantable cardioverter-defibrillator [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 noncardiovascular 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 nonischemic 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., pulmonary embolism, PAD).

CABG = coronary artery bypass graft; CV = cardiovascular; d = days; HF = heart failure; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

Appendix 5 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., pulmonary embolism, PAD).
- Length of stay is at least 24 h (or extends over a calendar date).

Appendix 6 Protocol amendment history

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

Amendment	Date	Main reason(s)
1	02 August 2018	To introduce the 6MWT sub-study to maximize knowledge gain and continue this efficacy assessment from the main study. Additionally, to include collection of MR proANP, research biomarker (optional), and NT-proBNP at prespecified visits and events.
2	16 May 2019	To correct the description of the Investigational Medicinal Product used in this study.
3	06 February 2020	• To align the strategy for subject enrollment into this open-label (OL) extension study due to premature termination of recruitment into the AC-055G202 SERENADE main study: • Eligible subjects may enroll into this OL extension study after remaining in the main study (AC-055G202) for at least 24 weeks • To remove evaluation of the efficacy assessments (i.e., Kansas City Cardiomyopathy Questionnaire, accelerometry, echocardiography, and blood sample collection for N terminal pro-brain natriuretic peptide [NT-proBNP], mid-regional pro-atrial natriuretic peptide [MR-proANP], and biomarkers) in an effort to simplify the study and reduce assessment burden for subjects and study site personnel.

Amendment	Date	Main reason(s)
		• To stop the 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. • To remove Clinical Event Committee (CEC) adjudication in line with AC-055G202 SERENADE main study global protocol Version 6. The CEC was appointed to review and adjudicate in a blinded fashion worsening heart failure (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 with the low occurrence of clinical events, which will not allow 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 create a single version of the SERENADE OL AC-055G203 protocol by incorporating Voluntary Harmonisation Procedure (VHP)-mandated changes into the global protocol version. VHP-mandated additions will only affect VHP countries and include the following: • Study termination at 5 years as one option described in Section 3.1.2; required monthly Liver Function Tests (LFTs) monitoring described in Section 7.2.4.1; and use of double-barrier contraception methods only when the use of highly effective measures, as described in Section 4.4.2, is medically contraindicated.
4	16 July 2020	• To update the exclusion criteria and 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.

Actelion Pharmaceuticals Ltd
Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A long-term, multicenter, single-arm, open-label extension of the SERENADE study, to assess the safety and efficacy of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease

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SERENADE OL

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

Protocol AC-055G203; Phase 2b

JNJ-67896062/ACT-064992 Macitentan

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Actelion Pharmaceuticals Ltd; Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

EudraCT NUMBER: 20118-001603-37

Status: Approved
Date: 2 July 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: D-20.204

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL [AC-055G203

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. Missed assessments/visits will be captured in the 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 case report form (CRF).

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.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- 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

    - 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 to be applied under exceptional circumstances (section 5.1.5.3), 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 applied. Safety laboratory testing should include AST/ALT and hemoglobin at minimum.

    - 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 perform all assessments that have been missed.

- Missed assessments/visits will be captured in the 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 or absence 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.4 (core ICF v.3) 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): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD

Note: If 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.