Janssen Research & Development

Statistical Analysis Plan

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

Protocol AC-055G203/ SERENADE-OL; Phase 2b

JNJ-67896062/ACT-064992 (macitentan)

Status: Approved
Date: 2 November 2021
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-RIM-574620, 1.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	2 November 2021	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) for study AC-055G203 / SERENADE OL, describes in detail the methods, conduct and content of statistical analyses of efficacy and safety endpoints planned for the final abbreviated Clinical Study Report (CSR).

This SAP refers to the documents listed in Table 2.

Table 2: Study Documents

Document	Version
Study Protocol AC-055G203 (SERENADE OL)	Final version 6 (EDMS-RIM-263261)
eCRF specifications	Final version 002

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM).

The DPS Part 1 document is prepared in line with this SAP to provide the outputs list and all the programming details necessary to implement the statistical analysis.

Study data tabulation model (SDTM) datasets of the AC-055G203 / SERENADE OL study and Analysis Data Model (ADaM) datasets from AC-055G202 / SERENADE DB, are used as source data for the statistical analyses.

The pooling of SERENADE DB and SERENADE OL means that data from the SERENADE DB will be concatenated with the data from the SERENADE OL study, for all participants regardless of enrollment in the SERENADE OL, with the aim to report the long-term safety and efficacy results in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease.

1.1. Objectives

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

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

1.2. Study Design

This is a multi-center, single-arm, OL Phase 2b extension study of the SERENADE study, designed to gather additional longer-term safety and efficacy data with macitentan 10 mg in subjects with HFpEF and PVD beyond the 52 weeks of treatment in the main double-blind SERENADE study (AC-055G202).

Approximately 112 subjects were expected to enter the OL study, which was conducted at the sites participating in the main study (ie, 77 sites in 17 countries).

See the protocol for further details on study design, visits and assessment schedule.

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 (excluded).

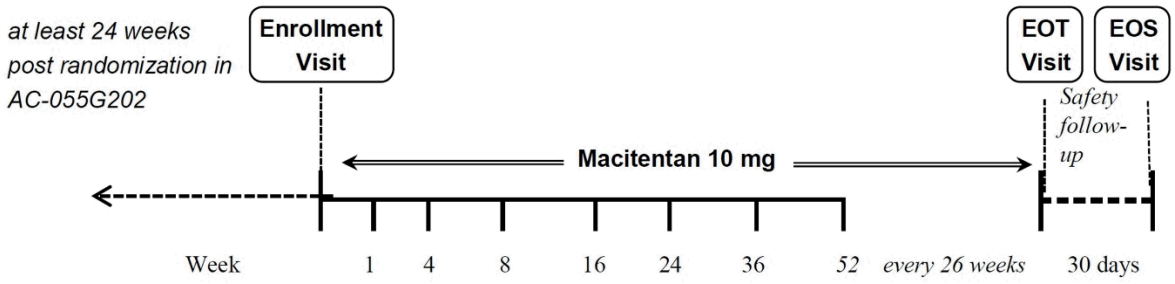
Treatment period: Starts with the administration of the first dose of OL study treatment and ends on the day of the last dose of OL study treatment.

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 transition from the main study to SERENADE OL is described in section 7.1.1. of the protocol.

The overall study design is depicted in Figure 1.

Figure 1: Study design



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

The schedule of visits and assessments can be found in the Table 3 below.

Table 3: 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 weeks (±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 (ie, 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 protocol 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.

2. STATISTICAL HYPOTHESES

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% 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.

The long-term efficacy will be explored based on select cohorts within 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 SERENADE study Clinical Study Report (CSR).

Safety variables will be analyzed using the Safety Set for the OL study. Adverse events and other selected safety variables during treatment with macitentan (eg, exposure and the following laboratory parameters: erythrocytes, hemoglobin, hematocrit, leukocytes, lymphocytes, neutrophils, platelets, AST, ALT, total bilirubin, alkaline phosphatase, MLAs and eGFR) will be analyzed on the Safety Initiated Set (all subjects who received double-blind macitentan treatment in the main study and/or in SERENADE OL).

3. SAMPLE SIZE DETERMINATION

The sample size for the SERENADE OL is 91 subjects.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

All the analysis sets are described in the protocol section 10.1.

Analysis Sets	**Description**
Open-Label Extension Enrolled Set (OLE)	The Open Label Extension enrolled (OLE) Set includes all subjects who were enrolled into the SERENADE OL (with answer 'YES' to the question 'Was the subject enrolled?' in the "Enrollment" form of the eCRF).
Full Analysis Set (FAS)	The Full Analysis Set includes all subjects randomized in the main double-blind study regardless of enrollment to SERENADE OL. In order to adhere to the intention-to-treat principle as much as possible subjects are evaluated according to the study treatment they have been assigned to at randomization (which may be different from the study treatment they have received).
SERENADE OL Safety Analysis Set (Safety Set)	All subjects who received at least one dose of OL treatment.
Safety Initiated Set	The Safety Initiated Set includes all subjects who received macitentan treatment in the DB period of 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.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Visit Windows

To allow analysis of data at the relevant planned (scheduled) visits during the treatment period, recorded assessments, including unscheduled ones, are re-assigned to the most appropriate visit according to the best fitting time window for that visit (see Table 4 and Table 5 below). Note that the visit windows are contiguous in order to retain all values in the analysis by time point.

Assessments for the analysis of the combined period MRI+DB+OL or DB+OL are reassigned according to the Table 5 time windows (based on MT Day and DB+OL Day respectively, see Section 5.1.2.7) while assessments performed during SERENADE OL study are reassigned, for the analysis of the OL period only, according to Table 4 (based on Treatment Day, see Section 5.1.2.7).

Table 4: Visit Windows for the OL period

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Safety and efficacy parameters	-	Baseline	<=1	1
	30	Week 4	2 to 42	28
	40	Week 8	43 to 84	56
	50	Week 16	85 to 140	112
	60	Week 24	141 to 210	168
	70	Week 36	211 to 308	252
	80	Week 52 - EOT	309 to 395	365
Safety and efficacy parameters (applicable only to VHP countries)	80	Week 52	309 to 454	365
	90	Week 78	455 to 636	546
	100	Week 104	637 to 818	728
	110	Week 130	819 to 1000	910
	120	Week 156	1001 to 1182	1092
	130	Week 182	1183 to 1364	1274
	140	Week 208	1365 to 1546	1456
	150	Week 234	1547 to 1728	1638
	160	Week 260 - EOT	>=1729	1820

*Number of days from the study treatment start date in OL.

Table 5: Visit Windows for the MRI+DB+OL/DB+OL period

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (MT/DB+OL Day)
Safety and efficacy parameters	-	Baseline	<=1	1
	-	Week 4	2 to 70	28
	-	Week 16	71 to 140	112
	-	Week 24	141 to 267	168
	-	Week 52	268 to 454	365
	-	Week 78	455 to 636	546
	-	Week 104	637 to 818	728
	-	Week 130	819 to 1000	910
	-	Week 156	1001 to 1182	1092
	-	Week 182	1183 to 1364	1274
	-	Week 208	1365 to 1546	1456
	-	Week 234	1547 to 1728	1638
	-	Week 260 - EOT	>=1729	1820

*Number of days from the MRI/DB treatment start date in the main study.

In the event that there is more than one value within the same time window, the value closest to the planned assessment date will be taken. In the event of equidistant values from the planned time point, the last assessment will be considered for the analyses. Where multiple assessments fall on the same day the latest is then used.

For laboratory values the central laboratory values are always selected in favor of any local laboratory value. If more than one value falls on the same date and time (and laboratory) then the one with the last sequential number in SDTM will be used.

Based on the SERENADE DB study results indicating no evidence of benefit of macitentan 10 mg treatment in patients with HFpEF and pulmonary vascular disease the Sponsor decided to stop the SERENADE OL study without option for continued access. For this reason, it is expected that follow-up will be varied across subjects with a few participants in the VHP countries (see Section 6.3, Appendix 3 for details) with data beyond Week 52. All subjects visit assessment information available will be considered up to their last follow-up visit.

5.1.2. Relevant time points, baseline and analyses periods

5.1.2.1. Signed informed consent

It is the date of signed informed consent collected in the “Informed Consent” CRF.

5.1.2.2. Enrollment date

For all the enrolled subjects (all subjects with answer ‘YES’ to the question ‘Was the subject enrolled?’ in the “Enrollment” CRF), it is the date of the Visit 1 / Enrollment.

5.1.2.3. OL Study treatment start date

It is the study treatment start date in OL, ie, the first day of intake of study treatment during the SERENADE OL. It is derived from the first treatment start date (in chronological order) in the ‘Study Treatment Log’.

5.1.2.4. Study treatment end (EOT) date

For participants in the SERENADE main study not enrolled in the SERENADE OL, it is the EOT date in the SERENADE main study.

For subjects enrolled in the SERENADE OL, this is the "Treatment end date" from the last interval, in chronological order, recorded in the 'Study Treatment Log' where the reason for treatment end is not temporary interrupted due/not due to an AE.

If missing or incomplete, rules in Section 5.1.4 are followed.

5.1.2.5. End of study (EOS) date

Subjects completing the EOS visit, the date of the visit is the EOS date.

For subjects who died during the study, the EOS date is "Date of death" collected in "Death" form.

For all other subjects, the EOS date is collected in "Study discontinuation" CRF form according to the reason for discontinuation as follows:

- Lost to follow-up = date of last successful contact.
- Subject decision/ withdrawal of consent = date of subject decision
- Physician decision = date of physician decision
- Sponsor decision = Date subject was informed of sponsor decision.

5.1.2.6. Baseline

Baseline for the SERENADE OL

The baseline for a given measurement in the SERENADE OL is the last value assessed ≤ to the start date of treatment in the SERENADE OL. If unscheduled/re-test visits are performed on the day of treatment start, the available value of the last unscheduled/re-test visit on treatment start date is considered as baseline.

Baseline of the SERENADE main study (for the analysis in the DB+OL period)

The baseline for a given measurement in the SERENADE main study was the last value assessed ≤ to the start date of double-blind treatment in the SERENADE main study. If unscheduled/re-test visits were performed on the day of treatment start, the available value of the last unscheduled/re-test visit on treatment start date were considered as baseline.

Macitentan baseline (for the analysis in the MRI+DB+OL period)

The macitentan baseline is defined as the last assessment prior to macitentan initiation, ie:

- for patients who received macitentan already in the double-blind period of the SERENADE main study, baseline is the last available assessment performed on or prior to the macitentan run-in period start date.

- for patients who received placebo in the double-blind period of the SERENADE main study and received macitentan in the SERENADE OL, baseline is the last available assessment performed on or prior to SERENADE OL treatment start date.

Macitentan baseline is the last non-missing value obtained ≤ to the start of macitentan intake in the main study or SERENADE OL, ie, ≤ MT Day 1.

5.1.2.7. Treatment Day, DB+OL Day and Macitentan Day

The **Treatment Day** (Day) is the number of days elapsed since the treatment start date in the SERENADE OL plus 1 (as treatment start date in OL is considered Day 1).

The **Double-blind plus open-label treatment Day** (DB+OL Day) is the number of days elapsed since the double-blind treatment start date in the SERENADE main study plus 1 (double-blind treatment start date is considered Day 1).

The **Macitentan Day** (MT Day) is the number of days elapsed since the day of first dose of macitentan, ie:

- for patients who received macitentan already in the double-blind period of the SERENADE main study is the number of days elapsed since the macitentan run-in treatment start date plus 1 (as macitentan run-in treatment start date is considered MT Day 1).

- for patients who who received placebo in the double-blind period of the main study and entered SERENADE OL, it is the number of days elapsed since the OL treatment start date plus 1 (as OL treatment start date is considered MT Day 1). For these patients, MT Day = Treatment Day.

Therefore, the treatment day, the double-blind plus open-label treatment day and the macitentan day are always different from 0.

5.1.2.8. Open-label treatment-emergent period (OL period)

Is the period between the study treatment start date in OL (see definition in Section 5.1.2.3) excluded up to the EOT date (see definition in Section 5.1.2.4) + 30 days.

5.1.2.9. Macitentan treatment-emergent period (MRI+DB+OL period)

The macitentan treatment-emergent period is defined as the period from the first intake of macitentan (for subjects who received macitentan already in the double-blind period of the SERENADE main study this is the date of their first dose of macitentan run-in treatment whereas, in all the other cases, this is the study treatment start date in the SERENADE OL, Section 5.1.2.3) excluded up to EOT + 30 days.

5.1.2.10. Double-blind plus open-label treatment-emergent period (DB+OL period)

The double-blind plus open-label treatment-emergent period is defined as the period between the double-blind treatment start date in the SERENADE main study (excluded) up to the EOS (Section 5.1.2.5) date in the SERENADE OL study.

5.1.3. Conversion rules

- eGFR =175 x $(S_{Cr})^{-1.154}$ x$(age)^{-0.203}$ x0.742 [if female] x1.212 [if Black]

where S_{Cr} (standardized serum creatinine) is expressed in mg/dL, age in years.

5.1.4. Imputation Rules for missing/incomplete date and time fields

This section describes some general principles to be followed in the case of missing or incomplete dates/times.

In the following, 'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. The earliest and the latest dates refer to the first or last date, respectively, when ordered in sequence. Other sources should be considered for possible dates including death date and date of withdrawal from study when determining possible dates.

Type of date/time	Date/time is incomplete	Date/time is missing
For determining treatment duration and emergent period		
Treatment start date in SERENADE OL	- Day missing: Replaced by day of the enrollment date. In case the day of enrollment is in the previous month, replace the day by 1. - Day and month are missing: replace entirely by the enrollment date.	Replace entirely by the enrollment date, if evidence the subject was treated in the study. Otherwise is considered not treated. Evidence includes Visit > Visit 1 other than study discontinuation. Treatment end date present.
Treatment end date (EOT)	Use the earliest date between the: upper limit EOS date of death date of last successful contact	Use the earliest date between the: EOS date of death date of last successful contact.
End of Study (EOS)	The upper limit.	Raw extraction date.
Adverse events		
AE resolution date	The upper limit.	No approximation, the AE is considered as ongoing in the analysis.

Type of date/time	Date/time is incomplete	Date/time is missing
AE onset date *Note these rules are applicable only to AE recorded in the "Adverse Event" CRF form, not in the "Ongoing Adverse Event from AC-055G202" CRF form (for these events the onset date is to be retrieved from the SERENADE database).*	If the resolution date of the AE is on or after the study treatment start date or is missing: if the treatment start falls in the range of possible dates, this date is used. Otherwise, the lower limit is used.	If the end date of the AE is on or after the treatment start date or is missing: the treatment start date is used.
Medications		
Concomitant medication end date	The upper limit unless the medication started prior to study treatment start and 'Ongoing at start of OLE enrollment?' is ticked 'No', and the study treatment start falls in the range of possible dates then it is replaced with treatment start date - 1.	No replacement
Concomitant medication start date	If the end date of the medication is not before the study treatment start date and if the study treatment start date falls in the range of possible dates, the study treatment start date is used. In all the other cases, the lower limit is used.	No replacement, the medication is considered to have started before the study treatment start date.
Death date	Use the lower limit.	No replacement.

5.1.5. General rules for data presentations

This section describes the general rules applied for all data displays.

Unless otherwise specified in this document:

- All listings will be sorted by geographical region (order according to Section 6.3), country (alphabetical order), site, subject number and when appropriate by visit / date of assessment. All data collected will be displayed, including unscheduled visits (if any). When applicable, listings will be presented by "DB-Placebo", "DB-Macitentan" treatment groups.
- In summary tables and graphical representations, results will be displayed overall and by randomized treatment group in the main SERENADE study.
- The absolute change from baseline to Visit/Week X is defined as the difference between the post-baseline Visit X value and the OL or macitentan baseline value.

- Number of non-missing observations, mean, standard deviation (SD), minimum, Q1, median, Q3 and maximum for continuous variables.
- Data will be summarized in tables including: number of non-missing observations, frequency with percentage per category (percentages based on the number of non-missing observations) for categorical variables.
- Number of events, number of censored observations, number of subjects at risk, and KM estimates of the survival function, hazard ratios and corresponding 90% confidence intervals will be displayed for time-to-event variables.
- Where appropriate the efficacy and safety analyses will be performed presenting summaries overall and by DB study treatment received (DB-macitentan or DB-placebo.
- When applicable, in summary tables, columns will be presented in the following order from left to right: “DB-Placebo”, “DB-Macitentan” and “Total”.

5.2. Participant Dispositions

The following definitions are relevant to the disposition information:

5.2.1. Screened subjects and screening failures

No screening will be performed in the SERENADE OL study.

5.2.2. Study and Study treatment disposition

5.2.2.1. Study treatment discontinuation

Premature discontinuation will be collected in the “Study Treatment Log” CRF and identified as those with a treatment end date and associated reason ‘What was the reason for treatment end?’ answered ‘Premature Discontinuation’.

The reason for study treatment discontinuation will be taken from the ‘Premature Discontinuation of Study Treatment’ CRF, full list of reasons is as follows:

- Death
- Lost to follow-up
- Pre-specified study treatment discontinuation criteria
- Subject decision (AE, Lack of efficacy, No reason provided, Other)
- Physician decision (AE, Lack of efficacy, Other)
- Sponsor decision (Study termination, Other).

Subjects are evaluated by the investigator for completion of treatment via the CRF (“Study Treatment Log”) where the question ‘What was the reason for treatment end?’ is answered ‘Completed as per protocol’.

5.2.2.2. Study discontinuation

Subjects who prematurely discontinued the study are those with some entry in the "Study Discontinuation" eCRF form.

For subjects who prematurely discontinued the study, the reasons for study discontinuation are reported on the same "Study Discontinuation" CRF form and are as follows:

- Death
- Lost to follow-up
- Subject decision/Withdrawal of consent (AE, Lack of efficacy, No reason provided, Other)
- Physician decision (AE, Lack of efficacy, Other)
- Sponsor decision (Study termination, Other).

The date of study discontinuation corresponds to the reason; date of death (as entered in the "Death" CRF); date of last successful contact for subjects lost to follow up; date of subject decision, physician decision or when the subject was informed of sponsor decision.

Disposition information analysis

The following disposition information will be summarized, presenting the number and percent of subjects:

- Enrolled
- Enrolled in VHP countries (see Appendix 3)
- Received OL treatment
- Completed treatment
- Completed Study.

Listings of subjects will be provided for the following categories:

- unmet eligibility criteria
- prematurely withdrawn from the treatment (with reasons for premature treatment withdrawal)
- prematurely withdrawn from the study (with reasons for premature study withdrawal).

The number of subjects in each analysis set will be summarized by "DB-Placebo", "DB-Macitentan" treatment groups and overall. Subject membership in the different analysis sets will be provided in a listing.

5.3. Primary Endpoint Analysis

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

5.3.1. Definition of Endpoints

Safety endpoints are defined in section 6.2 of the protocol as:

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

All safety endpoints will be analyzed on the Safety Set during the open-label treatment-emergent period (OL period, see definition in Section 5.1.2.8) and when specified on the Safety Initiated Set during the macitentan treatment-emergent period (MRI+DB+OL period, see definition in Section 5.1.2.9).

5.3.1.1. All cause-deaths up to 30 days after study treatment discontinuation

The date/time of death and associated primary cause are recorded in the CRF "Death" form.

The original terms used by the investigator to describe death (ie, primary cause of death) are assigned PTs for classification and tabulation using latest implemented version of MedDRA.

Additional classification of primary cause of death is performed by the investigator based on pre-specified causes (CV vs. non-CV) available in the same CRF.

Treatment-emergent deaths are any death occurred during the open-label/macitentan treatment-emergent period.

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

All-cause hospitalizations as reported in the dedicated eCRF form "Hospitalization".

Treatment-emergent hospitalizations are those occurred during the open-label/macitentan treatment-emergent period.

5.3.1.3. Adverse events

An adverse event (AE) is defined as any event reported by the investigator in the "Adverse Event" CRF form. All AEs that occur after signing of the ICF and up to 30 days after study treatment

discontinuation or worsening in intensity of AEs started in the SERENADE main study are reported in the CRF "Adverse Event".

Note: events reported in the "Ongoing Adverse Event from AC-055G202" CRF form will be analyzed separately (Section 5.5.1.3).

The original terms used by the investigators to describe AEs are assigned preferred terms (PT) for classification and tabulation using the latest implemented version of MedDRA.

5.3.1.3.1. Treatment-emergent adverse events

Treatment-emergent AEs are defined as any AE that started during the open-label/macitentan treatment-emergent period, including the treatment start date.

5.3.1.3.2. Serious adverse events

An AE is considered serious if the tick box 'Yes' for 'Serious?' is checked on the AE CRF. If the information on seriousness is missing, the AE is assumed to be a SAE for the purpose of the summaries.

Treatment-emergent SAEs (TESAE) are determined as TEAEs (Section 5.3.1.3.1).

5.3.1.3.3. Adverse events leading to discontinuation of study treatment

An AE is considered as leading to discontinuation of study treatment if the tick box 'Drug withdrawn' of 'Action taken with study treatment' is checked on the "Adverse Event" CRF.

5.3.1.4. Clinical Laboratory Tests

Hematology and chemistry tests are performed at Visit 1/Enrollment, Visit 3/W4, EOT and EOS. In between Visit 4/W8 and EOT, monthly AST/ALT monitoring is recommended. Unscheduled assessments may be performed at any time during the study if appropriate based on the investigator judgment.

Data are evaluated in International system of units (SI units) unless specified otherwise as provided by the central laboratory. In case of local laboratory, values are provided in conventional units and converted to SI units. The tests converted to SI are available in SDTM for the analysis.

Note: Laboratory results recorded as '< xxx' (or similar with ≤, >, or ≥) will be considered as 'xxx' for analysis, e.g., a result for ALT of '< 1' is considered as 1 for the analysis. The values are listed including the < or > sign.

For the analysis, local laboratory values are included in the calculation of Marked Laboratory Abnormalities (Section 5.3.1.4.1). All assessments recorded after study treatment start date in SERENADE OL (Section 5.1.2.3) up to EOT (Section 5.1.2.4) + 30 days will be assigned to the most appropriate study visit according to the best fitting time-window for that assessment as detailed in Section 5.1.1. If more than one value for a laboratory parameter is assessed on the same day, from central and local laboratory, the value from the central laboratory is considered for the

analysis. If more than one value falls on the same date and time (and laboratory) then the one with the last sequential number in SDTM will be used.

Laboratory parameters include:

Hematology:

- Hemoglobin (SI Unit: g/L; Conventional unit: g/dL)
- Hematocrit (SI Unit: L/L; Conventional unit: %)
- Erythrocyte count (reticulocyte count) (SI Unit: 10^{12}/L; Conventional unit: 10^6/µL)
- Leukocytes count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
- Neutrophils count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
- Lymphocytes count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
- Monocytes count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
- Eosinophils count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
- Basophils count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)
- Platelet count (SI Unit: 10^9/L; Conventional unit: 10^3/µL)

Chemistry:

- ALT (U/L)
- AST (U/L)
- Alkaline phosphatase (U/L)
- Total and direct bilirubin (SI unit: µmol/L; Conventional unit: mg/dL)
- Creatinine (SI unit: µmol/L; Conventional unit: mg/dL)
- Blood urea nitrogen, BUN (SI unit: mmol/L; Conventional unit: mg/dL)
- Uric acid (SI unit: µmol/L; Conventional unit: mg/dL)
- Sodium, potassium, chloride, calcium, magnesium (mmol/L)
- Total protein, albumin (SI unit: g/L; conventional unit: g/L)
- Albumin / Globulins ratio
- estimated Glomerular Filtration Rate (mL/min/1.73m^2) using the Modification of Diet in Renal Disease formula.

The absolute observed value (during the OL period, during the MRI+DB+OL period and during the DB+OL period separately) and the change from baseline (see Section 5.1.2.6) to each post-baseline visit for some **selected laboratory parameters** (ie, erythrocytes, hemoglobin, hematocrit, leukocytes, lymphocytes, neutrophils, platelets, AST, ALT, total bilirubin and alkaline phosphatase) are defined as:

Change from baseline = value at Visit X - (value at baseline).

5.3.1.4.1. Marked laboratory abnormalities (MLAs)

MLAs are all marked laboratory abnormalities which occur during the open-label treatment-emergent period (on Safety Set) and during the macitentan treatment-emergent period (on Safety Initiated Set), that were not present at baseline (see Section 5.1.2.6).

The following marked laboratory abnormalities (MLA) are derived according to the protocol.

Table 6: Definition of marked laboratory abnormalities

Parameter	LL marked	LLL marked	HH marked	HHH marked
Hematology				
Hemoglobin *(baseline value within normal range or below LLN)*	< 100 g/L	< 80 g/L	> 20 g/L above ULN	> 40 g/L above ULN
Hemoglobin *(baseline value > ULN)*	< 100 g/L	< 80 g/L	> 20 g/L above baseline	> 40 g/L above baseline
Hematocrit	< 0.28 L/L for females < 0.32 L/L for males	< 0.20 L/L	> 0.55 L/L for females > 0.60 L/L for males	> 0.65 L/L
Leukocytes	< 3.0×10^9/L	< 2.0×10^9/L	> 20.0×10^9/L	> 100.0×10^9/L
Neutrophils	< 1.5×10^9/L	< 1.0×10^9/L	NA	NA
Lymphocytes	< 0.8×10^9/L	< 0.5×10^9/L	> 4.0×10^9/L	> 20.0×10^9/L
Eosinophils	NA	NA	> $5x10^9$/L	NA
Platelets	< 75×10^9/L	< 50×10^9/L	> 600×10^9/L	> 999×10^9/L
Chemistry				
ALT*	NA	NA	> 3 × ULN	> 5 × ULN
AST*	NA	NA	> 3 × ULN	> 5 × ULN
Alkaline phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Total bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine *(baseline value within normal range or below LLN)*	NA	NA	> 1.5 × ULN	> 3 × ULN
Creatinine *(baseline value > ULN)*	NA	NA	> 1.5 × above baseline	> 3 × above baseline
BUN	NA	NA	> 2.5 × ULN	> 5 × ULN
Uric acid	NA	NA	> 590 µmol/L	> 720 µmol/L
Sodium	NA	< 130 mmol/L	> 150 mmol/L	> 155 mmol/L

Parameter	LL marked	LLL marked	HH marked	HHH marked
Potassium	< 3.2 mmol/L	< 3.0 mmol/L	> 5.5 mmol/L	> 6.0 mmol/L
Magnesium	< 0.5 mmol/L	< 0.4 mmol/L	NA	> 1.23 mmol/L
Calcium	< 2.0 mmol/L	< 1.75 mmol/L	> 2.9 mmol/L	> 3.1 mmol/L
Albumin	< 30 g/L	< 20 g/L	NA	NA

* For ALT and AST, additional threshold (HHHH) are reported namely > 8 × ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen;
LLN = lower limit of the normal range; NA = not applicable; ULN = upper limit of the normal range.

5.3.1.5. Change from baseline in Glomerular Filtration Rate (eGFR) up to 30 days after study treatment discontinuation

The estimated Glomerular Filtration Rate (mL/min/1.73m^2) using the Modification of Diet in Renal Disease formula is assessed at all visits with laboratory test (see Section 5.3.1.4).

Unscheduled visits may be performed at any time during the study if appropriate based on the investigator judgment.

As described in laboratory Section 5.3.1.4, the assessments will be assigned to the most appropriate study visit. Data are evaluated as provided by the central laboratory.

The change in eGFR from baseline to each visit is defined as: value at Visit X - (value at baseline).

5.3.1.6. Vital signs

Vital signs (systolic and diastolic blood pressures [SBP and DBP], pulse rate) and body weight are measured pre-dose at all visits and reported in the "Vital Signs" CRF. Triplicate SBP and DBP and radial pulse measurements are measured in a supine or sitting position. The average of the triplicate values [provided in SDTM] will be used for the analysis.

5.3.2. Estimand

- **Primary Trial Objective:** To describe the long-term safety of macitentan 10 mg in subjects with HFpEF and pulmonary vascular disease.
- **Population:** Safety Set (for the analysis of the OL treatment-emergent period) and Safety Initiated Set (for the analysis of the macitentan treatment-emergent period).
- **Study Intervention**: macitentan oral tablet, 10 mg once daily.
- **Variables:** safety endpoints defined in Section 5.3.1 up to 30 days after study treatment discontinuation.

- **Population-level Summary Measure:**
    - total number and frequency for count variables; absolute changes from baseline for continuous variables.
    - Absolute change from baseline for continuous variables.
- **Intercurrent Events:** study treatment and study discontinuation (for any reason). Treatment policy strategy (*the occurrence of the intercurrent event is irrelevant in defining the treatment event of interest*).

5.3.3. Analysis Methods

The analysis of the primary endpoints will be performed on the Safety Initiated Set for the MRI + DB + OL period and on the Safety Set for the OL period only.

5.3.3.1. All cause-deaths up to 30 days after study treatment discontinuation

All-cause death cases will be reported in a subject listing. Treatment-emergent deaths will be flagged accordingly.

A summary table reporting the incidence of treatment-emergent deaths will be provided. Number and percentages of deaths will be summarized together with the primary reason for death in descending order of incidence.

5.3.3.2. 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.

Individual listings will also be provided.

5.3.3.3. Adverse events

The following definitions are relevant for analyzing the adverse events occurred during the study:

- Frequency of adverse events. AEs reported more than once (as qualified by the same PT) for a participant are counted only once in the frequency table.
- Intensity of adverse events. For AEs reported more than once (as qualified by the same PT) for a participant with different intensities, the worst intensity is considered. In case of missing intensity, "*severe*" is imputed.
- Relationship of adverse events. Relationship to study treatment is defined as 'related' or 'not related'. An AE is considered related if the causality is checked as 'related' by the investigator. For treatment-emergent AEs reported more than once (as qualified by the same PT) for a participant, the worst relationship (ie, 'related') is considered. Adverse events with missing relationship are considered in any analysis as 'related'.

An overall summary table of AEs will be provided, containing number and percentages of participants having experienced at least 1 occurrence of the following categories of AEs:

- Treatment-emergent AEs

- Severe treatment-emergent AEs
- Treatment-emergent AEs related to study treatment
- AEs with fatal outcome
- Treatment-emergent serious AEs (SAEs)
- Treatment-emergent SAEs (TESAEs) related to study treatment
- AEs leading to premature discontinuation of study treatment.

5.3.3.3.1. Treatment-emergent adverse events

The number and percentage of subjects with at least one treatment-emergent AE will be tabulated separately on the Safety Set (for the OL period) and the Safety Initiated Set (for the combined MRI + DB + OL period) by:

• System Organ Class and Preferred Term within System Organ Class;

• Preferred Term.

The summary tables will be presented by DB study treatment received ("DB-macitentan" or "DB-placebo" and "Total") in descending order (eg, SOC and PT within each SOC with the highest number of occurrences appears first) in the "DB-macitentan" treatment group. Equal frequency of different SOC/PTs will be sorted in alphabetical order of the SOC/PT. NOT Classified terms will be ordered last, verbatim terms will be included in the listing only

Similarly, tables by PT will be provided by DB study treatment received in descending order of incidence in the "DB-macitentan" treatment group. Equal frequency of different SOC/PTs will be sorted in alphabetical order of PT.

Listings will be provided for all reported AEs including a flag for the treatment-emergent ones.

5.3.3.3.2. Serious adverse events

SAEs will be listed in the general AE listing and in a separate listing. Treatment-emergent SAEs will be flagged accordingly.

Treatment-emergent SAEs will be summarized by SOC and PT within each SOC and by PT.

5.3.3.3.3. Adverse events leading to premature discontinuations of study treatment

All AEs leading to premature discontinuation of study treatment will be included in the general AE listing and in a separate listing on the Safety Initiated Set.

All AEs leading to premature discontinuation of study treatment will be summarized similarly to treatment-emergent AEs by SOC and PT within each SOC and by PT.

5.3.3.4. Clinical Laboratory Tests

All hematology and chemistry parameters provided by the central and local laboratory will be displayed in listings, including those from unscheduled visits. Marked laboratory abnormalities will be flagged accordingly.

For Week 4, Week 8, Week 16, Week 24, Week 36, Week 52 in the OL period (Table 4 of Section 5.1.1), the selected laboratory test parameters defined in Section 5.3.1.4 will be summarized displaying descriptive statistics (if at least 10 participants are available) for:

- observed value at each visit specified
- absolute change from baseline to each visit.

In each evaluation, will be included only participants who had both the assessments at baseline and post baseline visit, on the Safety Set.

Similarly, the selected laboratory tests defined in Section 5.3.1.4 will be summarized by treatment group (and total) in the MRI+DB+OL period (Table 5 of Section 5.1.1) on the Safety Initiated Set and in the DB+OL period (Table 5 of Section 5.1.1) on the FAS.

5.3.3.4.1. Marked Laboratory Abnormalities (MLAs)

Marked laboratory abnormalities will be summarized for the OL period (on the Safety Set) and for the MRI+DB+OL period (on the Safety Initiated Set) providing their counts and percentages and number of participants with at least one treatment-emergent marked laboratory abnormality, for each parameter for which the marked laboratory abnormality is defined.

Percentages will be calculated as number of participants with at least one treatment-emergent MLA for the parameter under consideration divided by the number of participants with any post-baseline laboratory measurement.

Shifts from baseline to worst post-baseline abnormality category (during the OL period and the MRI+DB+OL period separately) up to EOT + 30 days will be summarized with frequencies of participants and percentages per category of shift. Categories considered are LLL, LL, L (L = below LLN), normal (between LLN and ULN), H (H = above ULN), HH, HHH. For baseline the category ‘Missing’ is also considered. Participants experiencing a worsening from baseline in two different directions (eg, going from normal at baseline once to H and once to L post-baseline) are counted in both directions.

The denominator for percentages is the number of participants with at least one post-baseline assessment in the considered period.

For the below selected parameters, values over time in the OL period, in the MRI+DB+OL period and in the DB+OL period will be summarized and plot on the Safety Set, on the Safety Initiated Set and on the FAS, respectively:

- Hematology:
    - Hemoglobin
    - Hematocrit
    - Erythrocytes
    - Leukocytes
    - Lymphocytes
    - Neutrophils
    - Platelets.
- Chemistry:
    - Alanine aminotransferase (ALT)
    - Aspartate aminotransferase (AST)
    - Alkaline phosphatase
    - Total bilirubin.

Summaries and plots will be provided by "DB-Placebo" and "DB-Macitentan" treatment groups.

5.3.3.5. Change from baseline in Glomerular Filtration Rate (eGFR) up to 30 days after study treatment discontinuation

Descriptive summary statistics by visit will be provided for observed values and absolute changes in eGFR from baseline to each post-baseline visit in the OL period and the MRI+DB+OL period separately (on the Safety Initiated Set).

Individual subject's listing will be provided on the Safety Initiated Set by "DB-Placebo", "DB-Macitentan" treatment groups.

5.3.3.6. Vital signs

Vital signs (blood pressure measurements, pulse rate) and body weight will be reported in a listing. Position (supine or sitting) and location (left or right arm) will be included in the listing.

SBP, DBP, pulse rate, and body weight will be summarized displaying descriptive statistics in the SERENADE OL on the Safety Set and the MRI+DB+OL period on the Safety Initiated Set for:

- observed value at each visit up to EOT + 30 days
- absolute change from baseline to each visit up to EOT + 30 days.

In each evaluation, only participants who had both the assessments at baseline and the considered post-baseline assessment will be included.

Vitals signs parameters will be analyzed regardless of the measurement position.

5.4. Exploratory Efficacy Endpoints Analysis

5.4.1. Definition of Endpoint(s)

There are no primary or secondary efficacy variables defined for SERENADE OL; exploratory efficacy variables as described in protocol section 10.2.2 are:

- Time to first occurrence of worsening of heart failure (WHF) 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
- NYHA FC (improved/worsened/stable) at each post-baseline assessment

The exploratory efficacy variables will be analyzed in the DB+OL period on the FAS.

Baseline (Section 5.1.2.6) for efficacy variables is defined as the last non-missing value observed among all measures, including the unscheduled ones, collected up to and including the double-blind treatment in the SERENADE main study.

All assessments recorded after the start of study treatment, including the unscheduled ones, will be assigned to the most appropriate study visit according to the best fitting time-window for that assessment as detailed in Section 5.1.1.

5.4.1.1. Time to first occurrence of worsening of heart failure (WHF) event

Occurrence of a WHF event is assessed by the investigator using the 2015 ACC/AHA definition [see protocol section 7.2.2.1 and protocol appendix 3 for details].

A WHF event includes HF death, hospitalization for WHF or an urgent visit for WHF. WHF events determined by the investigator are reported in the CRF.

Time to first occurrence of WHF event is expressed in weeks and calculated as the onset date of the first WHF event minus the double-blind treatment start date plus 1 or, for censored participants, as the censoring date (see below) minus the study treatment start date plus 1.

The onset date of the first WHF event is the earliest between the following three dates:

- the date of death reported on the ‘Death’ form in the CRF where classification of primary cause of death is ‘HF’;
- the earliest date of WHF hospitalization entered on a ‘WHF Event’ CRF for a WHF event type of ‘WHF Hospitalization’;
- the earliest date of urgent WHF visit entered on a ‘WHF Event’ CRF for a WHF event type of ‘Urgent WHF Visit’.

All worsening of heart failure events occurring are considered, irrespective of participants’ compliance to assigned therapies.

Participants without any worsening of heart failure event up to EOS are right-censored at EOS or if they are enrolled in the VHP countries at the earliest between the EOS date (see Section 5.1.2.5) and the upper limit of the Week 52 time window (see Section 5.1.1).

5.4.1.2. Time to first occurrence of heart failure (HF) death or HF hospitalization

The variable of interest is the time to first occurrence of HF death or HF hospitalization.

Occurrence of HF death and hospitalization events are assessed by the investigator and recorded in the CRF ("Death" form and "Hospitalization" form respectively).

HF deaths are all deaths with a primary reason of 'HF' entered into the 'Death' CRF.

HF hospitalization is defined per appendix 5 of the protocol as:

- Participant 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).

HF hospitalization are defined as the hospitalizations recorded on the 'Hospitalization' CRF where length of stay ≥ 1 day (end date - start date ≥ 1) **AND** primary diagnosis of HF determined as the following criterion selected in the CRF:

'HF' is specified where the main reason for hospitalization is cardiovascular = 'Yes'.

All HF hospitalizations and HF deaths with an admission / death date on or after study treatment start date are considered, irrespective of participants' compliance to assigned therapies.

Participants without any HF hospitalization or HF death up to EOS are right-censored at EOS or if they are enrolled in the VHP countries at the earliest between the EOS date (see Section 5.1.2.5) and the upper limit of the Week 52 time window (see Section 5.1.1).

Time to first occurrence of HF death or HF hospitalization is expressed in weeks and calculated as the onset date of the first HF death or HF hospitalization minus the double-blind treatment start date plus 1 or, for censored participants, as the censoring date (defined above) minus the double-blind treatment start date plus 1.

5.4.1.3. Time to first occurrence of cardiovascular (CV) death or CV hospitalization

The variable of interest is the time to first occurrence of cardiovascular (CV) death or CV hospitalization.

Occurrence of CV death and hospitalization events are assessed by the investigator and recorded in the CRF ("Death" form and "Hospitalization" form respectively).

CV deaths are all deaths with a primary reason of 'CV: Acute MI', 'CV: Sudden cardiac death', 'CV: HF', 'CV: Stroke', 'CV: Procedure', 'CV: Hemorrhage', or 'CV: Other' entered into the 'Death' CRF.

CV hospitalization is defined per appendix 5 of the protocol as:

- Participant 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 (eg, PE, PAD).
- Length of stay is at least 24 h (or extends over a calendar date).

CV Hospitalization are the hospitalizations recorded on the 'Hospitalization' CRF where length of stay ≥ 1 day (end date - start date ≥ 1) **AND** the primary diagnosis CV determined as the question 'Was the main reason for hospitalization cardiovascular?' ticked 'Yes'.

All CV hospitalizations and CV deaths with an admission / death date on or after the study treatment start date are considered, irrespective of participants' compliance to assigned therapies.

Participants without any CV hospitalization or CV death up to EOS are right-censored at EOS or if they are enrolled in the VHP countries at the earliest between the EOS date (see Section 5.1.2.5) and the upper limit of the Week 52 time window (see Section 5.1.1).

Time to first occurrence of CV death or CV hospitalization is expressed in weeks and calculated as the onset date of the first CV death or CV hospitalization minus the double-blind treatment start date plus 1 or, for censored participants, as the censoring date (defined above) minus the double-blind treatment start date plus 1.

5.4.1.4. NYHA FC (improved/worsened/stable) at each post baseline assessment

Changes from baseline in NYHA FC values (I=1, II=2, III=3, IV=4) are categorized as improved, worsened or stable at every post-baseline (see Section 5.1.2.6 for definition) assessment according to the following rules:

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

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

Participants who died (any cause) are classified as worsened (NYHA FC = V).

5.4.2. Estimand

- **Exploratory Trial Objective**: To explore the long-term efficacy of macitentan 10 mg.
- **Population:** Full Analysis Set.
- **Intervention:** Macitentan oral tablet, 10 mg once daily.
- **Variables**:
    - Time to first occurrence of worsening of heart failure event
    - The time to first occurrence of HF death or HF hospitalization.
    - The time to first occurrence of cardiovascular (CV) death or CV hospitalization.
    - NYHA FC (improved/worsened/stable) at each post baseline assessment.

- **Population-level Summary Measure**:
    - Kaplan-Meier estimates of events over time with 2-sided 90% CIs at relevant time-points for time-to-event variables.
    - NYHA FC: proportion (with 90% confidence limits [CLs]) of participants having improved, having worsened or being stable at each post-baseline visit.

- **Intercurrent Events:** study treatment and study discontinuation (for any reason). Treatment policy strategy (*the occurrence of the inter-current event is irrelevant in defining the treatment event of interest*).

5.4.3. Analysis Methods

The analysis of the exploratory efficacy variables will be performed on the FAS for the DB+OL period.

5.4.3.1.1. Time to first occurrence of worsening heart failure

All WHF events (see Section 5.4.1.1) and the time to first occurrence of WHF will be listed, irrespective of participants' compliance to assigned therapies on the FAS by "DB-Placebo", "DB-Macitentan" treatment groups.

If at least 10 participants will experience a WHF event, a summary table will be provided displaying the number of participants with WHF overall and by type of WHF. Results will be displayed overall and by randomized treatment group in the main SERENADE study.

The analyses will be conducted using Kaplan-Meier estimates of events over time including graphical representation.

The graphical representation follows the recommendations from Pocock (Pocock 2002). Two-sided 90% CIs at specific time points will be constructed, with confidence limits calculated using Greenwood's formula for the estimate of the standard error. Median time to event (as well as 25th and 75th percentiles) for each group will be provided with the corresponding two-sided CIs calculated using the method of Brookmeyer (Brookmeyer 1982).

Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at timepoints (12, 24, 36 and 52 weeks) and displayed in both a graphical (where the number of participants at risk is at least 10% of the total number of participants in the analysis set) and a tabular form. In addition, the number of participants at risk, the number of participants censored and the number of participants with event will be computed at each time-point.

5.4.3.1.2. Time to first occurrence 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 (see Section 5.4.1.2 for details).

As described in the previous section, Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at time points (12, 24, 36 and 52 weeks) and displayed in both a graphical (where the number of participants at risk is at least 10% of the total number of participants in the analysis set) and a tabular form. In addition, the number of participants at risk, the number of participants censored and the number of participants with event will be computed at each time point. Results will be displayed overall and by randomized treatment group in the main SERENADE study.

Time to first occurrence of HF death or hospitalization will be presented in a listing on the FAS by “DB-Placebo”, “DB-Macitentan” treatment groups.

5.4.3.1.3. Time to first occurrence 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 (see Section 5.4.1.3 for details).

As described in Section 5.4.3.1.1, Kaplan-Meier estimates will be calculated with 2-sided 90% CIs at time points (12, 24, 36 and 52 weeks) and displayed in both a graphical (where the number of participants at risk is at least 10% of the total number of participants in the analysis set) and a tabular form. In addition, the number of participants at risk, the number of participants censored and the number of participants with event will be computed at each time point. Results will be displayed overall and by randomized treatment group in the main SERENADE study.

Time to first occurrence of CV death or hospitalization will be presented in a listing on the FAS by “DB-Placebo”, “DB-Macitentan” treatment groups.

5.4.3.1.4. NYHA FC (improved/worsened/stable) at each post baseline assessment

A shift table will present the participants scores at baseline and any shift to the worst-case post baseline during the DB+OL period to determine any change (see Section 5.4.1.4) on the FAS.

The proportion of participants in each category will be calculated based on the number of participants in the analysis set.

All NYHA FC data (including unscheduled assessments) will be listed on the FAS by double-blind treatment group.

The proportion of participants having improved, having worsened or being stable at each post baseline visit will be summarized overall and by double-blind treatment group.

5.5. Other Safety Analyses

5.5.1. Other significant adverse events

5.5.1.1. AEs with fatal outcome

An AE with fatal outcome is any AE with Outcome = “Fatal” in CRF.

Treatment-emergent AEs with fatal outcome will be included in the AE listing. A separate listing will be provided for all participant AEs with fatal outcome.

Treatment-emergent AEs with fatal outcome will be summarized for the Safety Set and the Safety Initiated Set separately by SOC and PT within each SOC.

5.5.1.2. AEs of special interest (AESI)

All AESI and HAESI (see Section 6.8 for definition) will be summarized by PT.

For each area of clinical interest, treatment-emergent AEs of special interest will be summarized for the Safety Set and the Safety Initiated Set, presenting counts and percentages of participants having experienced at least one treatment-emergent AE of special interest by frequency of PT within each AESI/HAESI group. Separate listings will be provided for all AEs of special interest on the Safety Set and the Safety Initiated Set.

5.5.1.3. AEs continuing from AC-055G202 (SERENADE)

Adverse Events started in AC-055G202 (SERENADE) but still ongoing at Enrollment in AC-055G203 (SERENADE OL) are reported in the CRF form “Ongoing Adverse Event from AC-055G202”.

AEs continuing from SERENADE will be summarized separately from the AE occurred during SERENADE OL by SOC and PT within each SOC and by PT, for the Safety Set.

A separate listing will be provided for all AEs ongoing from SERENADE study.

5.5.1.4. Other AEs of Interest

Treatment-emergent thrombocytopenia and leukopenia will be summarized for the Safety Set and the Safety Initiated Set.

Cases with events of ‘thrombocytopenia/platelets decrease’ are defined as any event PT within either of the following MedDRA SMQs: ‘Haematopoietic thrombocytopenia’, or ‘Haematopoietic cytopenias affecting more than one type of blood cell’ (with the exception of 2 unspecific PTs: ‘Blood disorder’, ‘Blood count abnormal’) or if they contain an event with any MedDRA PT containing the text ‘thrombocytopenia’ or ‘thrombocytopenic’.

Cases with events of leukopenia are defined as any event PT within either of the following MedDRA SMQs: 'Haematopoietic leukopenia', or 'Haematopoietic cytopenias affecting more than one type of blood cell' (with the exception of two unspecific PTs: 'blood disorder', 'blood count abnormal').

5.5.2. Additional Safety Assessments

5.5.2.1.1. Additional liver test abnormalities

The following summaries will be conducted for liver tests and hemoglobin based on the OL period (the Safety Set) and the MRI+DB+OL period (the Safety Initiated Set):

- ALT and / or AST > 3 × ULN
- ALT and / or AST > 5 × ULN
- ALT and / or AST > 8 × ULN
- ALT and / or AST > 3 and ≤ 5 × ULN
- ALT and / or AST > 5 and ≤ 8 × ULN
- Total Bilirubin > 2 × ULN
- ALT and/or AST > 3 × ULN and associated (ie, at the same visit) increase in total bilirubin > 2 × ULN
- Hemoglobin ≥ 80 g/L and < 100 g/L
- Hemoglobin < 100 g/L and a decrease from baseline > 20 g/L
- A decrease in hemoglobin from baseline of > 20 g/L
- A decrease in hemoglobin from baseline of > 20 g/L and ≤ 50 g/L
- A decrease in hemoglobin from baseline of > 50 g/L

The categories "ALT and / or AST > 3 × ULN", "ALT and / or AST > 5 × ULN", "ALT and / or AST > 8 × ULN" are not mutually exclusive and participants may be counted in more than one category. The highest ALT or AST value at any time point in the period is considered in the evaluation of these categories, as defined above. The hemoglobin values will be summarized similarly, considering for the evaluation of the categories the lowest hemoglobin value at any time point in the period.

For the evaluation of liver test and hemoglobin abnormalities, measurements from unscheduled visits will be included. All participant with at least one treatment-emergent abnormality will be provided in a separate participant listing.

Treatment-emergent liver test and hemoglobin abnormalities will be summarized similarly to the MLAs (Section 5.3.3.4.1).

5.5.2.1.2. Physical Examination Findings

Physical examination is performed at all scheduled visits and any post baseline abnormalities or baseline conditions that worsened post baseline should be reported on the Adverse Events/Serious AEs forms.

5.5.2.1.3. Electrocardiogram

A standard 12-lead ECG is performed at Visit 1/Enrollment, Visit 6/W24, Visit 7/W36, EOT.

All assessments recorded after start of treatment (Section 5.1.2.3) will be assigned to the most appropriate study visit according to the best fitting time-window for that assessment as detailed in Section 5.1.1.

The ECGs are interpreted locally, and the presence of 'atrial fibrillation' or 'atrial flutter' or 'sinus rhythm' are recorded in the CRF ("12-Lead ECG" form). Unscheduled assessments may be performed at any time during the study if appropriate based on the investigator judgment.

The following variable is also defined:

Treatment-emergent qualitative ECG abnormalities (findings): defined as presence (yes/ no) of any finding (atrial fibrillation or atrial flutter or sinus rhythm) during the OL period. Defined as any finding and separately for each type.

Atrial fibrillation / flutter (AF) is defined as presence of any atrial finding (atrial fibrillation or atrial flutter).

If atrial fibrillation = yes or atrial flutter = yes then AF = yes. If both are missing then AF is missing, otherwise AF= No.

Note a participant cannot have sinus rhythm = Yes if AF= yes at a visit assessment. However, a participant may be assessed at a visit as having neither presence of AF nor sinus rhythm (SR), in this case the finding is categorized as "other". In the rare event any case of both SR and AF is found, AF will be chosen considering that SR is not a negative finding. Therefore, the findings at a visit are categorized as AF, SR or other.

The count and percentage of participants with presence of treatment-emergent qualitative finding (atrial fibrillation/atrial flutter) will be summarized in a shift table, for the Safety Set. These will be presented as shift from baseline. A listing will be also provided.

5.6. Other Analyses

5.6.1. Extent of Exposure

The exposure in the SERENADE OL study is evaluated in terms of study treatment duration including study treatment interruptions and then in terms of actual weeks exposed to study treatment, excluding any interruptions. The data are recorded in the "Study Treatment Log" CRF.

Study treatment interruptions in SERENADE OL: a participant is considered to have had a study treatment interruption if the reason for treatment end is either 'Temporarily interrupted due to an AE' or 'Temporarily interrupted not due to an AE'.

Duration of treatment (weeks) in SERENADE OL: time (in days) elapsed between the treatment start date (Section 5.1.2.3) and the treatment end date (Section 5.1.2.4) + 1 day divided by 7, regardless of any treatment interruptions, ie, [(treatment end - treatment start +1)/7].

In the case that the treatment end date is missing or a reason other than 'Premature discontinuation' or 'Completed as per protocol' is reported, then the duration of treatment is calculated applying the general rules in Section 5.1.4.

Exposure to macitentan treatment (weeks) in SERENADE OL: treatment duration adjusted for interruptions defined as:

Duration of treatment - Total Duration of Interruptions (TDI),

where TDI is defined as the sum of the durations of interruptions.

The **duration of interruption** (days) is the time elapsed between the Interruption Start Date and the Interruption End Date, i.e., (Interruption End Date - Interruption Start Date), where Interruption Start Date is the 'Study Treatment Log' End Date with corresponding reason for treatment end being 'temporarily interrupted'. Interruption End Date is the next chronological 'Study Treatment Log' Start Date after Interruption Start Date. In the event of partial or missing treatment start or end date, exposure is missing. If Interruption End Date cannot be derived as there is no next chronological 'Study Treatment Log' entry the exposure is missing.

Participant year exposure in SERENADE OL: is calculated by summing the duration of study treatment for all participants (days) divided by 365.25.

For the combined MRI+DB+OL period, the below variables are derived:

Cumulative duration of treatment (weeks): time (in days) elapsed between the macitentan treatment start date and end date + 1 day divided by 7, regardless of any treatment interruptions, ie, [(treatment end - treatment start +1)/7].

Cumulative participant year exposure: is calculated by summing the cumulative duration of treatment for all participants (days), then divided by 365.25.

The duration of treatment (including interruptions) as well as the study treatment exposure (excluding interruptions) and the exposure (patient years) in SERENADE OL will be summarized on the Safety Set. The treatment duration will be also summarized as a categorical variable, presenting the distribution of treatment duration by class interval (i.e., at least 4, 8, 16, 24, 32, 52 weeks) and displaying frequency counts and percentages of participants in each class interval if at least 10 participants are available.

Similarly, the cumulative duration of macitentan treatment (in the combined MRI+DB+OL period) will be summarized both as continuous and categorical variable using descriptive statistics on the Safety Initiated Set. Results will be displayed overall and by randomized treatment group in the main SERENADE study.

A listing of exposure and study treatment interruptions will be provided for the Safety Initiated Set by DB study treatment received (DB-macitentan or DB-placebo).

5.7. Interim Analyses

5.7.1. Data Monitoring Committee (DMC) or Other Review Board

No interim analyses are planned for the study.

An Independent Data Monitoring Committee (IDMC) will not be utilized for the SERENADE OL study.

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.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

6-MWD	6-minute walk distance
6-MWT	6-minute walk test
AE	Adverse event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Chemical
bpm	Beats per minute
BP	Blood pressure
BUN	Blood Urea Nitrogen
CEC	Clinical Event Committee
CDDM	Clinical Development Data Management
CRF	Case report form
CI	Confidence interval
CRO	Contract research organization
CLs	Confidence limit(s)
CSR	Clinical study report
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EF	Ejection Fraction
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End-of-study
EOT	End-of-treatment
ERA	Endothelin receptor antagonist
ESRD	End Stage Renal Disease
EudraCT	European Clinical Trial Database
FAS	Full Analysis Set
FC	Functional Class
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HDL	High-Density Lipoprotein
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
ILSDRB	Independent Liver Safety Data Review Board
IxRS	Interactive voice/web Recognition System
KM	Kaplan-Meier
LAV	Left Atrial Volume
LVEF	Left Ventricular Ejection Fraction
LDL	Low-Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
MLA	Marked Laboratory Abnormalities
MR-proANP	Mid-Regional pro-Atrial 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
PASP	Pulmonary Artery Systolic Pressure
PD	Protocol Deviation
PGA	Patient Global Assessment
PT	Preferred Term
PTOP	Post-Treatment Observation Period
PVD	Pulmonary Vascular Disease
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic Blood Pressure
SCR	Screened analysis set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	International system of units
SMQ	Standardised MedDRA Query
SOC	System organ class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper limit of the normal range
USA	United States of America
VHP	Voluntary Harmonization Procedure
WHF	Worsening of Hearth Failure
WHO	World Health Organization
WHO DDE	World Health Organization Drug Dictionary Enhanced

6.2. Appendix 2 Changes to Protocol-Planned Analyses

6.2.1. Changes to the analyses planned in the study protocol

6.2.1.1. Baseline

Section 10.1.6 of the protocol defines:

- baseline as the last non-missing assessment obtained **prior** to the start of study drug intake in SERENADE OL (OL Baseline)
- macitentan baseline as the last non-missing assessment obtained **prior** to the start of macitentan intake in the main study or SERENADE OL, respectively.

For both baselines, the definition used in this SAP is the last non-missing assessment obtained **before or on the day of the start of macitentan treatment**. This is to capture changes in safety after the first intake of macitentan and is in line with the approach followed with the main SERENADE CSR study.

6.2.1.2. Usage of the analysis sets

In protocol section 10.1.6 is stated 'The Safety Initiated Set is used for the analyses of adverse events and other select safety variables during treatment with macitentan'. The selected safety variables analyzed on this set will be exposure and the following laboratory parameters: erythrocytes, hemoglobin, hematocrit, leukocytes, lymphocytes, neutrophils, platelets, AST, ALT, total bilirubin, alkaline phosphatase, MLAs and eGFR.

6.2.2. Changes in the conduct of the study / data collection

The following protocol amendments were performed:

Protocol AC-055G203 Version 2, amendment 1 - 2 August 2018:

- To correct the description of the Investigational Medicinal Product used in this study.

Protocol AC-055G203 Version 3, amendment 2 - 16 May 2019:

- To introduce a new efficacy endpoint, the 6-minute walk distance (6MWD), assessed by the 6-minute walk test (6MWT), as part of a sub-study to assess the change from baseline in exercise capacity. This to maximize the knowledge gain from Phase 2 development, by informing on the potential benefits of macitentan treatment in a HFpEF subset that tolerates macitentan. The Borg Dyspnea Index was assessed after each 6MWT.
- To include the collection of mid-regional pro-atrial natriuretic peptide and a research biomarker (optional) sample at scheduled visits and at the time of a fluid retention or worsening heart failure event to continue the analysis from the main study.
- To include the collection of N-terminal pro-brain natriuretic peptide at the time of fluid retention or worsening heart failure event to support the Clinical Event Committee review.

Protocol AC-055G203 Version 4, amendment 3 - 6 February 2020:

- To align the strategy for participant enrollment into this open-label (OL) extension study due to premature termination of recruitment into the AC-055G202 SERENADE main study:

  – Eligible participants 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 (ie, 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 participants and study site personnel;
- 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 the Clinical Event Committee (CEC) adjudication in line with AC-055G202 SERENADE main study global protocol Version 6. 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. 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 of the protocol; required monthly Liver Function Tests (LFTs) monitoring described in section 7.2.4.1 of the protocol; use of double-barrier contraception methods only when the use of highly effective measures, as described in section 4.4.2 of the Global Protocol Version 4, is medically contraindicated.

Protocol AC-055G203 Version 5, amendment 4 - 16 July 2020:

The purpose of this amendment was 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.

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

Protocol AC-055G203 Version 6, amendment 5 - 26 November 2020:

The overall reasons to issue this protocol amendment were:

- to adapt to changed internal safety language and reporting processes,
- to align with TransCelerate template,
- to update information about post-treatment access program, study treatment storage conditions, forbidden medications, Actelion's policy for study data disclosure,
- to make minor editorial revisions and corrections.

Note: Only the main reasons for the protocol amendments are described.

6.2.3. Clarifications concerning endpoint definitions and related variables or statistical methods

6.2.3.1. Previous and concomitant medications

Section 5.2.1 of the protocol specifies definitions for a previous therapy and a study-concomitant therapy for the purpose of capturing these in the CRF. The definitions for previous therapy and treatment concomitant therapy are adapted in this SAP for the purpose of presenting summaries for reporting and interpreting the results in the CSR.

The SAP changes to the protocol are, in line with the analysis performed in the main SERENADE study CSR, as follows:

- Previous therapy is relative to first dose rather than enrollment visit.
- Treatment-concomitant therapy is considered with respect to the study treatment start instead of the enrollment visit.
- Study-concomitant therapy is not required for reporting of results in the CSR.

6.2.3.2. Exploratory efficacy variables, time to event analysis

Regarding the time to event analysis of the exploratory efficacy variables, the protocol states 'Participants without any event up to EOS are right-censored at their time of EOS'. It has been specified that, for the participants enrolled in the VHP countries (see Section 6.3), the censoring date will be the earliest between the EOS and the upper limit of the Week 52 time window (see Section 5.1.1). It is expected that the follow up will be varied across participants (from 52 Weeks up to 260 weeks in the VHP countries), thus this correction has been introduced to provide unbiased survival estimates.

6.2.3.3. Sub-study assessments (6MWD and Borg Dyspnea Index)

Under global protocol Version 3, participants could continue the participation in the SERENADE sub-study, designed to evaluate the long-term effect of macitentan on 6-minute walk distance (6MWD). Under global protocol version 4 the sub-study assessments were stopped as the number of subjects participating in the sub-study was too low to allow for meaningful interpretation of results. Data regarding the sub-study will not be part of this CSR reporting.

6.3. Appendix 3 Demographics and Baseline Characteristics

Demographic data at screening comprise age (years; continuous and categorical), sex, ethnicity, race, race and geographical region. Data are provided in the SDTM.DM dataset (for re-screened participants they are taken from the latest re-screening).

The following categories are defined for demographic variables:

- **Age (years)**: 18–64, 65–84, ≥ 85

Note the above categories for age are the same as those required for disclosure to EudraCT and ClinicalTrials.gov.

- **Race** (Black or African American / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander / Asian / White / Other / Not applicable)
- **Geographical region:** the following geographical regions are applicable:
  - Americas: North America (USA), South America (Argentina and Brazil);
  - Western Europe: Austria, Denmark, France, Germany, Spain, Sweden, United Kingdom. In addition, Israel;
  - Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia.

VHP countries for which the study termination was scheduled at 5 years are the following:

- Denmark, Germany, Hungary, Poland, Sweden, United Kingdom.

Table 7 presents the list of demographic variables that will be summarized, using descriptive statistics.

Table 7: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Categorical Variables	
Age (18-64 years, 65-84 years and >=85 years)	Frequency distribution with the number and percentage of participants in each category.
Race (Black or African American / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander / Asian / White / Other / Not applicable)	
Geographical region	

The SERENADE OL baseline disease characteristics are listed below:

New York Heart Association Functional Class - NYHA FC ("NYHA Functional Class" CRF).

Echocardiography (provided by central echocardiographic laboratory):

- **Left Ventricular Ejection Fraction (LVEF) [%]:** classified as ≥ 40 - <50 and ≥ 50%. These categories represent the mid-range EF and preserved EF. In the unexpected case we have LVEF < 40%, this sub-category will also be displayed.
- **Left Atrial Volume Index (LAVI)** [mL/m^2]
- **Lateral E/e'**
- **Pulmonary Artery Systolic Pressure (PASP)** [mmHg].

Laboratory:

- **Creatinine** ***(***µmol/L, *SI units)*
- **Estimated Glomerular Filtration Rate** (mL/min/1.73m^2) using the Modification of Diet in Renal Disease formula [see Section 5.1.3].

Other baseline characteristics include the following:

- **Renal function**: the following categories are defined for renal function based on the estimated glomerular filtration rate [eGFR (mL/min/1.73m^2)] from the abbreviated modification of diet in renal disease (MDRD) study:
  - Normal: ≥ 90
  - Mild Decrease: 60 – <90
  - Moderate Decrease: 30 – <60
  - Severe Decrease: 15 – <30
  - End Stage Renal Disease (ESRD): <15.

Table 8 presents the list of baseline disease characteristics variables that will be summarized using descriptive statistics.

Table 8: Baseline Disease Characteristics Variables

Continuous Variables	**Summary Type**
Left Ventricular Ejection Fraction (LVEF) [%]	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Left Atrial Volume Index (LAVI) [mL/m2]	
Lateral E/e'	
Pulmonary Artery Systolic Pressure (PASP) [mmHg]	
Creatinine (µmol/L, SI units)	
Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	
Categorical Variables	
NYHA FC	Frequency distribution with the number and percentage of participants in each category.
Renal function	

Renal function based on the eGFR (mL/min/1.73m^2) is summarized as both continuous and categorical.

Echocardiography summaries will be presented on the OLE set only in case there are at least 70% of the participants in the OLE set with available data.

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category:

- Protocol Deviation prior to and at enrollment
- Protocol Deviation during treatment period and follow-up
- Protocol Deviation related to COVID-19.

The analyses of PDs will be based on the OLE.

Major protocol deviations will be summarized by category, displaying counts and percentages of participants with at least one PD. The summary table will be sorted by category and frequency in descending order; if a tie occurs, the tied characteristics will be sorted alphabetically.

All reported PDs will be reported in a listing. Major PDs will be flagged accordingly.

6.5. Appendix 5 Prior and Concomitant Medications

All medications as collected in the "Previous / Concomitant Medication" CRF.

The original terms used by the investigators to describe medications are assigned preferred terms and anatomic therapeutic chemical (ATC) classification code using the latest version of the WHO Drug dictionary enhanced (WHO DDE).

Previous medication is defined as any medication that was started prior to start date of open-label study treatment (see definition in Section 5.1.2.3) and with an end date prior to the start date of study treatment or end date equal to the start date of study treatment with the flag 'Ongoing at start of OLE enrollment?' ticked "No".

If the end date is missing and the start date is prior to the date of open-label study treatment start, then the medication is considered as previous if 'Ongoing at start of OLE enrollment?' is ticked "No".

Study-treatment concomitant medications are all the medications that are ongoing at start of open-label study treatment or initiated on or after study treatment start date and up to study treatment end (EOT) date [Section 5.1.2.4] + 30 days (inclusive).

Rules for handling missing and partial dates are detailed in Section 5.1.4.

Diruetics are determined as detailed in the main SERENADE study CSR SAP (section 5.2.5.7), from all medications as collected on "Previous / Concomitant Medication" CRF.

Number and percentages of participants having taken at least one medication will be presented by Anatomic Therapeutic Chemical (ATC) class (level 4) and PT within each ATC class. All medications will be tabulated by ATC class, and individual preferred terms within each ATC class, for the OLE Set. ATC classes will be sorted by descending order of frequency; if the frequencies of ATC class are the same, alphabetical order will be used. The same rule applies for preferred terms within ATC class. Verbatim terms will be included in the listing only.

Previous medications and study-treatment concomitant medications will be summarized separately using descriptive statistics for categorical data.

All medications will be reported in a listing for the OLE Set, with flags to identify previous and study-treatment concomitant ones accordingly.

Diuretics will be listed in a separate listing.

6.6. Appendix 6 Medical History

Medical history is not applicable as this information (including specific medical history) is not collected in this SERENADE OL study.

Medical history data recorded in the database of the main SERENADE study will be used for listings on the OLE Set.

6.7. Appendix 7 Intervention Compliance

Study treatment compliance is based on the "Study Treatment Dispensing & Accountability" form. Study treatment compliance was 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 assessed at each visit by site personnel is calculated and entered in the CRF and is not (re-) calculated. The reasons for non-compliance since last visit are also collected in the CRF.

Study-treatment compliance in the SERENADE OL study will be summarized on the Safety Set, displaying counts and percentages of participants with compliance < 80%, 80%-120% and > 120%.

A listing of compliance for each visit will be also provided, containing the compliance values directly collected in "Study Treatment Dispensing & Accountability" form in CRF.

6.8. Appendix 8 Adverse Events of Special Interest

AEs of special interest (AESI) are identified below.

The definitions are based on a combination of MedDRA preferred terms (PTs) and SMQs (Standardized MedDRA Queries) which can be updated according to MedDRA version / SMQs updates.

<u>Oedema and fluid retention:</u>

- Any AE with PTs listed in the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" OR
- Any AE with PTs containing "Pulmonary congestion"
- excluding events with PTs containing "site"

Anaemia:

- Any AE with a PT within the SMQ "Haematopoietic erythropenia" OR
- Any AE with a PT within the SMQ "Haematopoietic cytopenias affecting more than one type of blood cell (excluding two unspecific PTs: "blood disorder", "blood count abnormal") OR
- an event with any MedDRA PT containing the text "anaemia".

Hepatic AEs of special interest (HAESI):

- Any AE with PT, SOC or HLGT containing the text specified in Table 9.

Table 9: Hepatic AE Terms

Term	Type
Acute graft versus host disease in liver	MedDRA PTs
Acute hepatic failure	
Acute on chronic liver failure	
Alanine aminotransferase	
Alanine aminotransferase abnormal	
Alanine aminotransferase increased	
Allergic hepatitis	
Alloimmune hepatitis	
Aspartate aminotransferase	
Aspartate aminotransferase abnormal	
Aspartate aminotransferase increased	
Asterixis	
Autoimmune hepatitis	
Biliary cirrhosis	
Bilirubin conjugated	
Bilirubin conjugated abnormal	
Bilirubin conjugated increased	
Blood bilirubin	
Blood bilirubin abnormal	
Blood bilirubin increased	
Cardiohepatic syndrome	
Cholestatic liver injury	
Chronic graft versus host disease in liver	
Chronic hepatic failure	
Chronic hepatitis	
Cirrhosis alcoholic	
Coma hepatic	
Cryptogenic cirrhosis	
Drug-induced liver injury	
Graft versus host disease in liver	
Hepatic cirrhosis	
Hepatic encephalopathy	
Hepatic encephalopathy prophylaxis	
Hepatic enzyme	
Hepatic enzyme abnormal	
Hepatic enzyme increased	
Hepatic failure	
Hepatic fibrosis	
Hepatic function abnormal	

Hepatic infiltration eosinophilic	
Hepatic necrosis	
Hepatic steato-fibrosis	
Hepatitis	
Hepatitis acute	
Hepatitis alcoholic	
Hepatitis cholestatic	
Hepatitis chronic active	
Hepatitis chronic persistent	
Hepatitis toxic	
Hepatocellular injury	
Hepatopulmonary syndrome	
Hepatorenal failure	
Hepatorenal syndrome	
Hepatotoxicity	
Hyperbilirubinaemia	
Hypertransaminasaemia	
Increased liver stiffness	
Ischaemic hepatitis	
Jaundice	
Jaundice cholestatic	
Jaundice hepatocellular	
Liver function test	
Liver function test abnormal	
Liver function test increased	
Liver injury	
Liver operation	
Liver transplant	
Lupoid hepatic cirrhosis	
Lupus hepatitis	
Minimal hepatic encephalopathy	
Mixed liver injury	
Multivisceral transplantation	
Nodular regenerative hyperplasia	
Non-alcoholic steatohepatitis	
Ocular icterus	
Portal fibrosis	
Primary biliary cholangitis	
Pseudocirrhosis	
Radiation hepatitis	
Renal and liver transplant	
Reye’s syndrome	
Reynold’s syndrome	
Steatohepatitis	
Subacute hepatic failure	
Transaminases	
Transaminases abnormal	
Transaminases increased	
Withdrawal hepatitis	
Yellow skin	
Hepatobiliary disorders	SOC Terms
Hepatobiliary investigations	HLGT Terms

7. REFERENCES

Brookmeyer R (Brookmeyer 1982), Crowley JA. CI for the median survival time. Biometrics. 1982;38:29-41.

Pocock SJ (Pocock 2002), Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. The Lancet. 2002;359:1686-9.