STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

AC-055-308 / MAESTRO-OL

Long-term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
BP	Blood pressure
CDDM	Clinical Development Data Management
CL	Confidence limit(s)
CSR	Clinical study report
DB	Double-blind
DBP	Diastolic blood pressure
eCRF	Electronic case report form
ENR	All-enrolled analysis set
EOS	End-of-Study
EOT	End-of-Treatment
ES	Eisenmenger Syndrome
ICE	Integrated computer environment
IXRS	Interactive Voice or Web Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MLA	Marked laboratory abnormalities
NT-pro-BNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
OL	Open-label

PD	Protocol deviation
PDE-5	Phosphodiesterase-5
PR	Pulse rate
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SI	Standard International
SMQ	Standardised MedDRA Query
SOC	System organ class
SpO_2	Saturation of peripheral oxygen
TLF	Tables Listings Figures
TTS	All-treated DB + OL set
ULN	Upper limit of the normal range
WHO	World Health Organization
WHODRUG	WHO drug dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the conduct and content of the statistical analyses of safety and efficacy data, for the purpose of the Clinical Study Report (CSR) of the open-label (OL) study AC-055-308 (MAESTRO-OL), hereafter referred to as the OL study.

Study data tabulation model (SDTM) datasets of the OL study provided by Actelion Clinical Development Data Management (CDDM) via the Integrated Computer Environment (ICE) system and Analysis Data Model datasets from the AC-055-305 (MAESTRO) CSR, hereafter referred to as the double-blind (DB) study, are used as source data for the statistical analyses.

A separate programming specification and conventions document has been prepared in line with this document to provide programming details necessary for implementing the statistical analysis.

2 STUDY DESIGN AND FLOW

AC-055-308 protocol version 4 [16 May 2014, D-14.170] is used as reference.

2.1 Study design

This trial is an OL, non-comparative, multi-center, Phase 3 extension study of protocol AC-055-305, which aims to assess the long-term safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome (ES).

A total of 226 subjects were randomized in a 1:1 ratio to macitentan 10 mg (n = 114) and placebo (n = 112) in the MAESTRO DB study. Subjects who completed the DB AC-055-305/MAESTRO study as scheduled (i.e., remained in the DB study up to Week 16, whether or not they were still taking study drug at the end of this period) were eligible to enter into the OL study, unless the DB treatment was discontinued for a safety issue. Subjects were rolled over from the AC-055-305 study to this OL study without knowledge of their previous study drug (macitentan or placebo).

The OL study is being conducted in 51 centers in 19 countries.

Protocol-mandated procedures and assessments are performed according to the visit and assessment schedule in Table 1.

2.2 Study visit and assessment schedule

See Table 1 for a detailed plan of the visit and assessment schedule [AC-055-308 protocol version 4, 16 May 2014, D-14.170].

Table 1 Visit and assessment schedule

PERIODS		**TREATMENT**						**FOLLOW-UP**	
VISITS	**Number**	**1**	**2**	**Monthly Lab & Safety Monitoring[5]**	**3, 4**	**5, 6, etc.**	**EOT**	**Safety follow-up / EOS**	**U1, 2,…**
	Name	**Enrollment[2]**	**Month 1**		**Month 6, Month 12**	**Month 18, Month 24, etc.**			**Unscheduled visits[6]**
	Time	**Day 1**	**Month 1 ± 1 week**	**Month 2 & every month thereafter up to EOT ± 1 week**	**Month 6 & Month 12 ± 2 weeks**	**Month 18 & every 6 months thereafter ± 2 weeks**	**Within 7 days after study drug disc.**	**30–33 days after study drug disc.**	**Anytime during the study**
Informed consent / assent		X							
Vital signs, body weight, physical examination		X	X		X	X	X		X[6]
Concomitant medications		X	X	X	X	X	X	X	X[6]
SpO_2		X			X		X		X[6]
WHO functional class / 6MWT/Borg dyspnea index		X			X		X		X[6]
Complete laboratory tests[1]		X[3]			X	X	X		X[6]
Serum pregnancy test / methods of contraception *(if applicable)*[4]		X[3, 8]	X	X	X[8]	X[8]	X[8]	X	X[6]
Hemoglobin[7]		X[3, 8]	X	X[7]	X[8]	X[8]	X[8]	X	X[6]
LT		X[3, 8]	X	X	X[8]	X[8]	X[8]	X	X[6]
Study drug dispensing		X		X[11]	X	X			
Study drug return					X	X	X		
AEs[9]		X	X	X	X	X	X	X	X[6]

PERIODS		**TREATMENT**						**FOLLOW-UP**	
VISITS	**Number**	**1**	**2**	**Monthly Lab & Safety Monitoring[5]**	**3, 4**	**5, 6, etc.**	**EOT**	**Safety follow-up / EOS**	**U1, 2,…**
	Name	**Enrollment[2]**	**Month 1**		**Month 6, Month 12**	**Month 18, Month 24, etc.**			**Unscheduled visits[6]**
	Time	**Day 1**	**Month 1 ± 1 week**	**Month 2 & every month thereafter up to EOT ± 1 week**	**Month 6 & Month 12 ± 2 weeks**	**Month 18 & every 6 months thereafter ± 2 weeks**	**Within 7 days after study drug disc.**	**30–33 days after study drug disc.**	**Anytime during the study**
SAEs[9]		X	X	X	X	X	X	X[10]	X[6]

1. Complete laboratory tests: hematology (including hemoglobin), blood chemistry (including LTs), and serum pregnancy test. Laboratory samples at all visits will be sent to and analyzed by the central laboratory.
2. The enrollment visit is combined with the Week 16 (i.e., Visit 6 for subjects who complete the 16 weeks of DB treatment, or Visit 6a for subjects who prematurely discontinue DB treatment) in the AC-055-305 study. Tests are not to be repeated if performed for the Visit 6 or Visit 6a of the AC-055-305 study but are to be reported in the eCRF of both studies (if applicable).
3. In order to check the eligibility of the subject on the day of Enrollment, local laboratory results are required in addition to the sample sent to the central laboratory for analysis.
4. Only concerns females of childbearing potential.
5. Whenever possible, the monthly laboratory samples will be collected at site and analyzed centrally. Site staff should take this opportunity to meet the subject to discuss any (S)AEs that could have occurred since previous visit, and assess the concomitant medications and methods of contraception (if applicable). However, under specific circumstances (e.g., subject lives far away from the site and cannot return every month), monthly laboratory samples could be collected in a local laboratory close to where the subject lives and analyzed centrally; in these cases, the assessment of (S)AEs should be done via a telephone call.
6. At any time during the study (between Enrollment and EOS visit) unscheduled site visits may be performed (based on investigator discretion). These include (but are not limited to) visits performed in case of safety concerns (e.g., new (S)AE, worsening of symptoms/assessment of 6MWD, adequate follow-up of any safety issues). Any study-specific procedures/assessments may be performed at an unscheduled visit, in which case the data will be collected in the eCRF.
7. Hemoglobin concentration will be measured every month during the first 6 months, every 3 months thereafter up to the EOT visit, and 30 days after study drug discontinuation (EOS visit).
8. Measured as part of the complete laboratory tests panel.
9. All new SAEs and AEs occurring from first dose of OL study drug up to 30 days after study drug discontinuation must be reported in this OL study.
10. New SAEs occurring after the 30-day follow-up period must be reported to the Actelion drug safety department, within 24 hours of the investigator's knowledge of the event, if considered causally related to previous exposure to the study medication by the investigator. They are reported on an SAE form but not on the eCRF.
11. Study drug may be dispensed on a monthly basis during monthly lab and safety monitoring.

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic Case Report Form; EOS = end-of-study; EOT = end-of-treatment; LT = liver test (liver aminotransferases [AST/ALT], alkaline phosphatase, total and direct bilirubin); OL = open-label; SAE = serious adverse event; SpO_2 = saturation of peripheral oxygen.

3 OBJECTIVES

This OL study aims to assess the long-term safety and tolerability of macitentan in subjects with ES beyond the treatment of the DB study, and to assess the long-term effect of macitentan on exercise capacity in this subject population.

3.1 Primary objective(s)

No primary endpoint is defined in this OL extension study.

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

As the MAESTRO DB study did not demonstrate a statistically significant effect of macitentan on the primary efficacy endpoint of exercise capacity in subjects with ES assessed at Week 16, for this OL study it was decided to minimize the number of analyses related to the exploratory efficacy endpoints. Therefore, the analyses of the "Change from baseline of the OL to Month 6 and Month 12" for the exploratory efficacy endpoints (i.e., 6-minute walk distance [6MWD], Borg dyspnea index, WHO Functional Class and saturation of peripheral oxygen [SpO_2]) as described in section 3.8.1 of the protocol have been removed [D-14.170].

The analyses of the efficacy endpoints will focus on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in the OL study. Summary tables will be created for absolute values, and change from DB baseline values. The change from DB baseline values will be plotted only for 6MWD.

In protocol section 5.2 the "Restricted all-enrolled set" is defined as all subjects enrolled in the OL study who received macitentan during the DB study; this set is used for efficacy analysis. Given that the efficacy analyses in this OL CSR will present the results as per treatment received during the DB period, and the analyses on the restricted all-enrolled set would therefore be redundant, it has then been decided not to present analyses based on this analysis set.

Per protocol, treatment-emergent marked laboratory abnormalities (MLAs) are analyzed up to EOT. For consistency across all safety endpoints in this study (i.e., with the treatment-emergent period reported for adverse events [AEs]), and with the MLA reporting in the DB study, MLAs will be analyzed up to End-of-Treatment (EOT) + 30 days. This revision ensures that any event/assessment performed after EOT, as well as any safety assessment performed beyond EOT, will be captured.

The analyses of liver enzymes have been revised to align with project-specific definitions for abnormal values.

Section 5.4.1 of the protocol states that deaths and the reason for death will be summarized in a similar manner to serious adverse events (SAEs), although deaths are not explicitly listed as an endpoint in section 3.8.2 of the protocol. This SAP clarifies that deaths are considered to be a safety endpoint to better characterize the safety profile.

AEs of special interest (AESI) are not described in the OL protocol; however, the analysis on AESIs are included in this SAP.

5 DEFINITIONS OF VARIABLES

The variable derivations and conventions are consistent (unless explicitly specified) with the AC-055-305/MAESTRO CSR SAP [redacted].

5.1 Screening failures

Subjects are not screened prior to entry in this OL extension study and no screening information is collected.

5.2 Subject characteristics

5.2.1 Demographics

With the exception of age at start of OL, all subject demographic characteristics will be taken from the DB study database. The following subject demographic characteristics will be reported: sex, age at start of OL (years), weight (kg), height (cm), body mass index (BMI [kg/m^2]), race, ethnicity, and geographical region.

The following age categories will be derived:

- **CSR categorization:** 12–17, 18–55, ≥ 56 years;
- **EudraCT categorization:** 12–17, 18–64, 65–84, ≥ 85 years.

Regions are defined as follows and subjects will be categorized depending on the countries involved in this OL study, as applicable:

- **Asia-Pacific**: China, Malaysia, Philippines, Vietnam;
- **Eastern Europe**: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia, Serbia;
- **Latin America**: Chile, Mexico;
- **North America**: Canada, USA;
- **Western Europe-Israel**: Austria, France, Germany, Greece, Israel, Portugal, South Africa, Spain, Turkey, United Kingdom.

5.2.2 Baseline disease characteristics

5.2.2.1 General characteristics

All subject baseline disease characteristics will be taken from the DB study database. The following baseline disease characteristics will be reported:

- Down Syndrome status (yes/no);
- Time from ES diagnosis (years) to the screening date of DB study;
- 6MWD (m);
- WHO functional class (I, II, III, IV);
- Borg dyspnea score (0–10);
- SpO2 at rest (%);
- Phosphodiesterase-5 (PDE-5) inhibitors (yes/no);
- Smoking behavior (never, former, current).

5.2.3 Medical history

No medical history information is collected as part of this OL protocol. Medical history information collected prior to entry into the DB study is reported in the DB clinical study report [redacted] and will not be replicated in this OL study report.

5.2.4 Previous and concomitant therapies

All therapies as collected in the "Concomitant medication" module of the OL electronic case report form (eCRF) including hormonal contraceptives (for females of childbearing potential only) collected in the dedicated module "Contraception methods". The original terms used by the investigators to describe therapies are assigned Preferred Terms (PTs) for classification and tabulation using the latest implemented WHODRUG version dictionary.

Rules for handling missing/incomplete start/end dates of medications are detailed in Section 11.7.

5.2.4.1 Previous therapies

A previous therapy is any therapy recorded on the "Concomitant medication" module of the OL eCRF for which the end date is prior to the date of enrollment visit in the OL study.

5.2.4.2 Study-concomitant therapies

Study-concomitant therapies are all therapies recorded on the "Concomitant medication" module of the OL eCRF:

- With "Ongoing at start of treatment?" answered "Yes" or with "Ongoing at last visit?" answered "Yes"; OR
- With the start date prior to the start of OL study (i.e., date of enrollment, see definition in Section 11.1) AND the end date on or after the start of study; OR
- With the start date on or after the start of study AND on or before the date of End-of-Study (EOS) visit [see definition in Section 11.2].

5.2.5 Other subject characteristics

5.2.5.1 Contraceptive methods

The use of contraceptive methods (for females of childbearing potential only) are collected in the dedicated OL eCRF module. For each contraceptive method used, the start date, end date, combination with spermicide (Y/N), ongoing at start of treatment (Y/N), and ongoing at last visit (Y/N) are collected. For hormonal contraceptives, the generic name, dose, units, and frequency are also collected.

In addition, for females of childbearing potential only, serum pregnancy tests (i.e., choriogonadotropin beta) are performed at the same visits as the other laboratory tests. The results are provided by the central laboratory.

5.3 Study treatment exposure and compliance

5.3.1 Exposure

The exposure is evaluated first in terms of study treatment duration including study treatment interruptions. The study treatment duration of macitentan, irrespective of study treatment interruptions, is derived in weeks as:

(study treatment end date − study treatment start date + 1) / 7.

Study treatment duration of macitentan will be derived over the following periods:

- **Combined DB + OL period**
  where study treatment start date = macitentan treatment start date [see Section 11.3.3], and study treatment end date = macitentan treatment end date [see Section 11.4.3];
- **OL only period**
  where study treatment start date = OL treatment start date [see Section 11.3.2], and study treatment end date = OL treatment end date [see Section 11.4.2].

In addition, the study treatment exposure is evaluated in terms of actual weeks exposed to study treatment, excluding any temporary interruptions [see details below in Section 5.3.4].

5.3.2 Compliance with study treatment

The compliance during the OL study is calculated by CDDM according to the formula in section 3.5 of the protocol (see below) and recorded in the "Drug accountability" module of the eCRF:

> Compliance during OL = (number of tablets taken / total number of tablets that should have been taken during the treatment period) * 100.

Compliance (in %) with study treatment is calculated at each dispensing/return visit as well as for the whole OL treatment period. Reasons for non-compliance since last visit are also collected.

The number of tablets dispensed/returned during the DB study is recorded in the drug accountability dataset for the DB study.

The compliance to macitentan treatment during the combined DB + OL period will be derived in the analysis datasets using the same formula as specified above.

5.3.3 Study treatment discontinuation

Study treatment discontinuations include all subjects, i.e., those who prematurely discontinued and those who completed treatment as per protocol.

Study treatment discontinuations are collected in the "Exposure" eCRF module per the reason associated with the study treatment end date [see definition in Section 11.4.2].

Subjects who completed the study treatment as per protocol are those with the question "What was the reason for treatment end?" answered "COMPLETED AS PER PROTOCOL".

Subjects who prematurely discontinued study treatment are those with the question "What was the reason for treatment end?" answered "PREMATURE PERMANENT DISCONTINUATION".

Detailed reasons for study treatment discontinuations are collected in the "Premature Permanent Study Drug Discontinuation" eCRF module (i.e., Death, Lost to follow-up, Physician's decision/AE, Physician's decision/Other, Subject's or legal representative's decision to withdraw consent from treatment only, Subject's or legal representative's decision to withdraw consent from study, Subject's or legal representative's decision/Other, Sponsor's decision/Study discontinuation, Sponsor's decision/Other, Other specify).

5.3.4 Study treatment adjustments or interruptions

Study treatment dose adjustments are not permitted per protocol.

Per protocol section 3.4.1, study treatment interruptions should be avoided where possible, and interruptions exceeding two consecutive weeks must lead to permanent discontinuation of study treatment.

Any temporary interruptions in macitentan intake are collected in the 'Exposure' eCRF module for the OL study and in the 'Study drug log' eCRF module for the DB study.

The exposure to macitentan is calculated for both the combined DB + OL period and the OL-only period as:

> Study treatment duration of macitentan during the treatment period – total duration of interruptions during the period treatment.

Where total duration of interruptions is the sum of all treatment interruptions, and the duration of each treatment interruption is calculated as:

> Treatment start date following interruption – treatment end date preceding interruption –1.

5.4 Study discontinuation

Study discontinuation includes all subjects, i.e., those who prematurely discontinued and those who completed the study as per protocol.

Subjects who completed the study as per protocol are those with the question "Did the subject complete the study?" answered "Yes" in the "End of Study" eCRF module.

Subjects who discontinued prematurely are those with the question "Did the subject complete the study?" answered "No".

For subjects who discontinued study prematurely, the detailed reason for study discontinuation is collected, i.e., Death, Lost to follow-up, Physician's decision (Specify), Sponsor's decision/Study discontinuation, Sponsor's decision/Other, Subject's or legal representative's decision to withdraw consent from study, Subject's or legal representative's decision/Other.

EOS date is collected in the "End of Study" eCRF module.

5.5 Efficacy variables

Efficacy endpoints of the study are defined as:

- Change from DB baseline [see Section 11.7] to Week 16 in the DB study, Month 6 and Month 12 in the OL study, in:
  - Exercise capacity, as measured by the 6MWD;
  - WHO functional class;
  - Dyspnea (assessed by the Borg dyspnea index);
  - Oxygen saturation, assessed by pulse oximetry: SpO2 at rest before the 6-minute walk test (6MWT).

No re-mapping is performed for this analysis: unscheduled visits, if any, are presented only in the individual subject listings.

Absolute change from baseline for all continuous efficacy endpoints is calculated as:

Post-baseline value − baseline value,

The following will be derived for all efficacy endpoints:

- Change from DB baseline to each post-baseline scheduled visit (i.e., Week 16 of DB study, Month 6 and Month 12 of the OL study);

5.5.1 Efficacy variable: 6MWD

The 6MWT is performed at Enrollment visit (Visit 1), Visit 3/Month 6, Visit 4/Month 12, and EOT. Unscheduled visits may be performed at any time during the study if necessary.

Absolute change from baseline for the 6MWD is calculated as described in Section 5.5 above.

5.5.2 Efficacy variable: WHO functional class

The WHO functional class is assessed at Enrollment visit (Visit 1), Visit 3/Month 6, Visit 4/Month 12, and EOT. Unscheduled visits may be performed at any time during the study if necessary.

Change from baseline to Week 16 in the DB study, and to Month 6 and Month 12 in the OL study, in WHO functional class is categorized as follows:

- Improvement (i.e., shift to lower class [e.g., from III to II]) or
- Worsening (i.e., shift to higher class [e.g., from III to IV]) or
- Unchanged (i.e., no shift).

5.5.3 Efficacy variable: Borg dyspnea index

The Borg dyspnea index is evaluated after each 6MWT at Enrollment visit (Visit 1), Visit 3/Month 6, Visit 4/Month 12, and EOT. Unscheduled visits may be performed at any time during the study if necessary. Dyspnea is rated on a scale from '0' to '10'.

Absolute change from baseline for the Borg dyspnea index is calculated as described in Section 5.5 above.

5.5.4 Efficacy variable: SpO_2

Oxygen saturation is assessed by pulse oximetry (SpO_2). SpO_2 is measured at rest before the 6MWT at Enrollment visit (Visit 1), Visit 3/Month 6, Visit 4/Month 12, and EOT.

Absolute change from baseline for the SpO_2 is calculated as described in Section 5.5 above.

5.6 Safety variables

The following safety variables will be evaluated:

- Treatment-emergent AEs up to 30 days after study treatment discontinuation;
- AEs leading to premature discontinuation of study treatment;
- Deaths up to 30 days after study treatment discontinuation;
- Treatment-emergent SAEs up to 30 days after study treatment discontinuation;
- Treatment-emergent AESIs up to 30 days after study treatment discontinuation
- Treatment-emergent MLAs up to 30 days after study treatment discontinuation;
- Change from baseline up to 30 days after study treatment discontinuation in laboratory parameters;
- Treatment-emergent alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) abnormality (> 3 × upper limit of normal [ULN]; > 5 × ULN; > 8 × ULN) associated or not with total bilirubin > 2 × ULN up to 30 days after study treatment discontinuation;
- Change from baseline up to 30 days after study treatment discontinuation in vital signs (arterial blood pressure [BP], pulse rate) and body weight.

Unless otherwise specified, the following apply throughout this section:

- All safety variables are summarized over the combined DB + OL period [see Section 11.5.3], using the all-treated DB + OL set.

- The study treatment start date as defined in Section 11.3.3 (i.e., date of first intake of macitentan) and the study treatment end date / study treatment discontinuation (EOT) defined in Section 11.4.3 are used.
- The observation period for each individual subject starts at the time of the first administration of macitentan [see Section 11.3.3] and ends with the permanent discontinuation of macitentan [see Section 11.4.3] + 30 days, regardless of study (i.e., DB or OL).
- The baseline for a given measurement is the macitentan baseline as defined in Section 11.3.3.
- The last post-baseline value up to 30 days after study treatment discontinuation [see Section 11.4.3], including values from unscheduled visits, is evaluated in the relevant analysis.

5.6.1 Adverse events

An AE is defined as any term reported by the investigator in the "Adverse Event" eCRF module. The original terms used by the investigators to describe AEs are assigned PTs for classification and tabulation using the latest implemented MedDRA version dictionary. If events are coded with an older MedDRA version, these events will be re-coded using the latest implemented MedDRA version dictionary.

5.6.1.1 Treatment-emergent AEs

Treatment-emergent AEs are all AEs with onset on or after the study treatment start date and up to the study treatment discontinuation plus 30 days.

5.6.1.2 Frequency of treatment-emergent AEs

Except where otherwise specified, the counting of treatment-emergent AEs in the summary table is handled as follows:

- Subjects who experienced the same AE (as qualified by the same PT[s]) more than once are counted only once.

5.6.1.3 Intensity of treatment-emergent AEs

Subjects who experienced the same AE (as qualified by the same PT[s]) more than once, but with different intensities, are counted only once, with the maximum intensity in the corresponding analysis. In case of missing intensity, *"severe"* is imputed.

5.6.1.4 Relationship of treatment-emergent AEs

Relationship to study treatment is defined as 'related' or 'not related'. An AE is considered related if the question 'Is there a reasonable possibility that the Adverse Event was related to the use of study drug?' is answered 'Yes'. For AEs reported more than

once (as qualified by the same PT[s]) within a subject, the worst relationship (i.e., related) is considered. AEs with a missing relationship are considered as related in any analysis.

5.6.2 Deaths

The date of death and associated primary cause are recorded in the "Death Form" of the eCRF. The original terms used by the investigators to describe deaths (i.e., primary cause) are assigned PTs for classification and tabulation using the latest implemented MedDRA version dictionary.

Treatment-emergent deaths are all deaths with the date on or after the study treatment start date and up to the date of study treatment discontinuation plus 30 days.

5.6.3 Serious adverse events

An SAE is any AE with the question "Serious?" answered "Yes" by the investigator.

SAEs leading to hospitalization are any SAEs with the question "Did the adverse event require subject hospitalization" answered "Yes" by the investigator.

Treatment-emergent SAEs are all SAEs with onset on or after the study treatment start date and up to the date of study treatment discontinuation plus 30 days.

For the disclosure of the results to EudraCT and ClinicalTrials.gov, SAEs during the OL study will be summarized.

Treatment-emergent SAEs during the OL study are all SAEs with onset on or after the OL treatment start date [see Section 11.3.2] and up to the OL treatment end date [see Section 11.4.2] plus 30 days.

5.6.4 Adverse events leading to premature discontinuation of study treatment

An AE leading to premature discontinuation of study treatment is defined as any AE with "Action taken with study drug" reported as "Permanently discontinued" by the investigator.

5.6.5 Other significant adverse events

5.6.5.1 AEs with fatal outcome

An AE/SAE with fatal outcome is any AE/SAE with "Outcome" reported as "Death" by the investigator.

Treatment-emergent AEs with fatal outcome are those with onset on or after the study treatment start date and up to the study treatment discontinuation plus 30 days.

5.6.5.2 AEs of special interest (AESI)

Standardized MedDRA Queries (SMQs) are available in SDTM.

- "Anaemia"

Treatment-emergent AEs with PTs within the SMQs "Haematopoietic erythropenia (SMQ)" OR "Haematopoietic cytopenias affecting more than one type of blood cell (SMQ)" (with the exception of two unspecific PTs: "blood disorder", "blood count abnormal") OR an event with any MedDRA PT containing the text "anaemia"

- "Hypotension"

Treatment-emergent AEs with one of the following PTs:

- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure immeasurable
- Blood pressure orthostatic decreased
- Blood pressure systolic decreased
- Diastolic hypotension
- Hypotension
- Orthostatic hypotension
- Procedural hypotension
- Mean arterial pressure decreased

- "Oedema and fluid overload"

Treatment-emergent AEs with PTs listed in the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" or with PT equal to "Pulmonary congestion", excluding any PT containing the text "site"

5.6.5.3 Non-serious AEs

For the disclosure of the results to EudraCT and ClinicalTrials.gov, non-serious AEs will be summarized.

A non-serious AE is any AE with the question "Serious?" answered "No" by the investigator.

Treatment-emergent non-serious AEs are all non-serious AEs with onset on or after the OL treatment start date [see Section 11.3.2] and up to the OL treatment end date [see Section 11.4.2] plus 30 days.

5.6.6 Vital signs and body weight

Vital signs are measured at all scheduled visits (i.e., Visit 1/Enrollment, Visit 2/Month 1, each 6-monthly visit, and EOT) in a supine or sitting position. Unscheduled visits may be performed at any time during the study if necessary. BP measurements are collected in the "Vital Signs" eCRF modules and include:

- *Systolic blood pressure* (SBP) in mmHg
- *Diastolic blood pressure* (DBP) in mmHg
- *Pulse rate* (PR) in beats per minute.

Body weight (kg) is collected at the same visits in the "Vital Signs" eCRF module.

The absolute change from macitentan baseline at each post-baseline scheduled visit (i.e., Visit 3/Week 4, Visit 4/Week 8, Visit 5/Week 12, and Visit 6/Week 16/EOT in the DB study, and Visit 2/Month 1, each 6-monthly visit, and EOT in the OL study) and last value up to 30 days after study treatment discontinuation for vital signs and body weight is calculated as:

(post-baseline value) − (value at macitentan baseline).

5.6.7 Electrocardiogram

Not applicable.

5.6.8 Laboratory

Complete laboratory parameters will be measured at enrollment (Visit 1), each 6-monthly visit, and EOT. Unscheduled visits may be performed at any time during the study if necessary.

Data are evaluated in Standard International (SI) units as provided by the central laboratory. In case of a local laboratory, values are converted in SI according to the Actelion OTH-000005 QS document. The tests converted in SI are available in SDTM for the analysis. All values reported as below or above the limit of detection (e.g., '< 3', '> 100') are substituted with the limit of detection (e.g., '< 3', is substituted by '3') for the purpose of the analysis. The values are listed including the < or > sign.

Data (i.e., hemoglobin values collected for the calculation of hemodynamic parameters) from cardiac catheterization are not included in any analysis.

In the event that more than one value for a laboratory parameter is assessed on the same day, both from central and local laboratory, the value from the central laboratory is considered for the analysis.

The absolute change from baseline at each post-baseline scheduled visit (i.e., Visit 3/Week 4, Visit 4/Week 8, Visit 5/Week 12, and Visit 6/Week 16/EOT in the DB study, and Visit 2/Month 1, each 6-monthly visit, and EOT in the OL study) and last value up to 30 days after study treatment discontinuation for laboratory parameters is calculated as:

(post-baseline value) − (value at macitentan baseline).

Laboratory parameters include:

- Hematology:
  - Hemoglobin (g/L)
  - Hematocrit (L/L)
  - Erythrocytes (10^{12}/L)
  - Leukocytes (10^{9}/L)
  - Platelets (10^{9}/L)
- Clinical Chemistry:
  - ALT (U/L)
  - AST (U/L)
  - Alkaline phosphatase (U/L)
  - Bilirubin (umol/L)
  - Direct bilirubin (umol/L)
  - Creatinine (umol/L)
  - Blood urea nitrogen (mmol/L)
  - Uric acid
  - Glucose (mmol/L)
  - Sodium (mmol/L)
  - Potassium (mmol/L)
  - Magnesium (mmol/L)
  - Calcium (mmol/L)
  - Albumin (g/L).

Liver tests (ALT, AST, alkaline phosphatase, total and direct bilirubin) are also assessed at Safety follow-up.

5.6.8.1 MLAs

The following MLAs are derived according to the sponsor's internal guidelines (OTH-000005).

Treatment-emergent MLAs are all MLAs with onset after the study treatment start and up to 30 days after study treatment discontinuation, that were not present at baseline.

For hemoglobin and creatinine (HH/HHH categories, only), treatment-emergent MLAs are those occurring after study treatment start and up to 30 days after study treatment discontinuation, as it is not possible to have HH or HHH flags at baseline per definition of the abnormality.

Table 2 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	> 5×10^9/L	NA
Platelets	< 75×10^9/L	< 50×10^9/L	> 600×10^9/L	> 999×10^9/L
Clinical 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

Glucose	< 3.0 mmol/L	< 2.2 mmol/L	> 8.9 mmol/L	> 13.9 mmol/L
Sodium	NA	< 130 mmol/L	> 150 mmol/L	> 155 mmol/L
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
Urate	NA	NA	> 590 µmol/L	> 720 µmol/L
Albumin	< 30 g/L	< 20 g/L	NA	NA

* For ALT and AST, additional threshold (HHHH) are to be 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.

5.6.8.2 Additional liver and hemoglobin laboratory abnormalities

The following elevated liver test abnormalities are defined:

- (ALT > 3 × ULN) **OR** (AST > 3 × ULN)
- (ALT > 5 × ULN) **OR** (AST > 5 × ULN)
- (ALT > 8 × ULN) **OR** (AST > 8 × ULN)
- Total bilirubin > 2 × ULN
- {(ALT > 3 × ULN) **OR** (AST > 3 × ULN)} **AND** (Total Bilirubin > 2 × ULN at any time)

If a subject has observations in different categories, he/she will be counted once in the worst category (i.e., the highest ALT, AST or total bilirubin values). If a subject has more than 1 observation within the same category, the subject will be counted once in that category. A supportive listing will be provided and will present all abnormal liver test data. Treatment emergent results will be flagged.

Treatment-emergent liver test laboratory abnormalities are those which occur after the study treatment start and up to 30 days after study treatment discontinuation, that were not present at baseline.

The following hemoglobin abnormalities are defined:

- Hemoglobin ≤ 80 g/L
- Hemoglobin > 80 and ≤ 100 g/L
- Hemoglobin decrease from baseline ≥ 20 g/L and < 50 g/L

- Hemoglobin decrease from baseline ≥ 50 g/L
- Hemoglobin < 100 g/L and concurrent (i.e., at the same time) decrease from baseline ≥ 20 g/L.

Treatment-emergent hemoglobin laboratory abnormalities are those which occur after the study treatment start and up to 30 days after study treatment discontinuation, that were not present at baseline (except for the decreases from baseline, which cannot be present at baseline per definition).

The lowest hemoglobin value / maximum decrease from baseline at any post-baseline time point of assessment up to 30 days after study treatment discontinuation is considered, as defined above.

5.6.9 Other safety variables

5.6.9.1 Physical examination

Physical examination is performed at all scheduled visits, collected in the dedicated module of the eCRF "Physical Examination" with general assessment performed. If an abnormality is found (i.e., Result = "Abnormal"), further details describing the signs and symptoms related to the abnormality are specified. The abnormality is clinically significant if the question "Clinically significant" is answered "Yes".

6 DEFINITION OF PROTOCOL DEVIATIONS

The description of each protocol deviation (PD) is agreed in the sponsor protocol deviation code list. According to this document, each PD is classified as important or not and categorized as follows:

- PDs before OL enrollment
- PDs at OL study entry (enrolled in IXRS)
- PDs during OL treatment period and follow-up

The data are available in SDTM.

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 All-enrolled set

The All-enrolled analysis set (ENR) includes all subjects enrolled in this AC-055-308 OL study (i.e., with a date of enrollment), whether or not they took at least one dose of macitentan during the OL study.

7.1.2 All-treated DB + OL set

The All-treated DB + OL set (TTS) comprises the union of:

(i) All subjects who received at least one dose of macitentan in this AC-055-308 OL study AND

(ii) All subjects who received macitentan during the AC-055-305 / MAESTRO study and were not enrolled in the OL study.

7.2 Usage of the analysis sets

Table 3 Overview of the different analysis sets and their usage

Analyses	All-enrolled set	All-treated DB + OL set
Subject disposition	✓	✓
Protocol deviations	✓	
Demographic characteristics	✓	
Baseline disease characteristics	✓	
Previous and concomitant therapies	✓	
Other subject characteristics	✓	
Study treatment exposure / discontinuations	✓	✓
Study discontinuation	✓	
Efficacy endpoints	✓	
Safety endpoints		✓
Demographic and baseline disease characteristics, other baseline characteristics, protocol deviation and efficacy listings	✓	
Disposition, safety listing		✓

DB = double-blind; OL = open-label.

8 DEFINITION OF SUBGROUPS

Not applicable.

9 GENERAL STATISTICAL METHODOLOGY

SAS (Statistical Analysis System®) version 9.3 is used for all the statistical analyses.

This section describes in general terms the statistical analysis methods which are applied in the subsequent sections.

9.1 Statistical methods for efficacy data

For each DB treatment group and overall (as applicable), efficacy data are summarized (tables or figures) at specified time points of assessments by appropriate descriptive statistics displaying:

- For continuous variables: number of non-missing observations, mean, standard deviation (SD), median, first and third quartile, minimum and maximum.
- For dichotomous variables: proportion of subjects in each category together with the 2-sided 95% confidence limits (CLs) (i.e., according to Clopper-Pearson formula).
- For categorical variables: a shift table from baseline to Month 6 and Month 12. The proportion of subjects having improvement/worsening are presented, together with the 2-sided 95% CLs (i.e., Clopper-Pearson formula).

9.2 Statistical methods for safety data

For each DB treatment group and overall, subject characteristics and safety data are summarized (tables or figures) by appropriate descriptive statistics displaying:

- For continuous variables: number of non-missing observations, mean, SD, median, first and third quartile (Q3), minimum and maximum.
- For dichotomous/categorical variables; number of non-missing observations, frequency and percentages for the two categories. Denominators for percentages are the number of non-missing observations in the analysis set and treatment group under evaluation, unless otherwise specified.
- Number of missing values are displayed only if > 0 and as follows:
  - For continuous variables after the n (number of non-missing observations)
  - For dichotomous/categorical variables after the last category.

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

No hypothesis testing will be performed; hence no p-values will be presented. All efficacy analyses are considered exploratory.

10.2 General rules for data presentations

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

Unless otherwise specified in this document:

- All listings are sorted by country, site, treatment group received during DB study, subject number and when appropriate by visit / date of assessment. All data collected are displayed, including unscheduled visits (if any).

- All summaries on the All-enrolled set and the All-treated DB + OL set will be presented overall and by DB treatment group (treatment received during DB study), i.e., Previously on DB macitentan and Previously on DB placebo.
- In summary tables, columns will be presented in the following order from left to right: "DB-Macitentan", "DB-Placebo" and "Total".

10.3 Display of subject disposition, protocol deviations and analysis sets

10.3.1 Subject disposition

Subject disposition is summarized on the All-enrolled set.

Counts and percentages of subjects enrolled in the OL study by country and site within each country are presented by DB treatment group and overall. The summary table is sorted by geographical region (i.e., Asia-Pacific, Eastern Europe, Latin America, North America, Western Europe-Israel-South Africa).

A summary table is provided for the OL study to display the following information by DB treatment group and overall:

- Counts of subjects enrolled;
- Counts of subjects treated (who received at least one dose of study treatment);
- Counts of subjects who completed study treatment [see definition in Section 5.3.3];
- Counts of subjects who prematurely discontinued study treatment [see definition in Section 5.3.3];
- Counts of subjects who completed study [see definition in Section 5.4];
- Counts of subjects who prematurely discontinued study [see definition in Section 5.4].

A separate summary table is provided for the OL study to display, by DB treatment group and overall:

- Counts and percentages of subjects who prematurely discontinued from the study [see definition in Section 5.4]
- Reason associated with premature discontinuation from the study [see definition in Section 5.4].

For subjects who prematurely discontinued study treatment and/or prematurely discontinued from the OL study, the EOT status and the EOS status with associated EOT and EOS dates, together with reasons for discontinuation, are reported in a subject listing.

10.3.2 Protocol deviations

Protocol deviations are summarized by category [see Section 6], displaying counts and percentages of subjects with at least one PD by DB treatment group and overall. A similar table is presented for important protocol deviations.

Protocol deviations are summarized on the All-enrolled set.

All reported PDs [as defined in Section 6] are reported in a subject listing. Important PDs are flagged accordingly.

10.3.3 Analysis sets

A table displaying counts and percentages of subjects included in each analysis is provided.

A listing displaying in which analysis sets each subject participates is provided.

Refer to Section 7 for the definition of analysis sets.

10.4 Analyses of subject characteristics

10.4.1 Demographics

Demographic characteristics are summarized on the All-enrolled set.

Continuous and categorical demographic characteristics [see definition in Section 5.2.1] are summarized by DB treatment group and overall, using descriptive statistics.

Age categories (12–17, 18–64, 65–84, $\geq$ 85 years) are also provided in a separate summary table by DB treatment group and overall for the disclosure of the results to EudraCT and ClinicalTrials.gov.

All demographic data as defined in Section 5.2.1 are reported in a subject listing.

10.4.2 Baseline disease characteristics

Baseline disease characteristics are summarized on the All-enrolled set.

Continuous and categorical baseline disease characteristics [see definition in Section 5.2.2.1] are summarized, by DB treatment group and overall, using descriptive statistics.

In addition to tabulations, all data are reported in a subject listing.

10.4.3 Medical history

Not applicable.

10.4.4 Previous and concomitant therapies

Study-concomitant therapies and previous therapies are summarized on the All-enrolled set.

Counts and percentages of subjects having taken at least one concomitant therapy [see definition in Section 5.2.4.1] are presented, separately, by Anatomic Therapeutic Chemical (ATC) class and PT within each ATC class, as well as by PT. The summary tables are presented in descending order according to the incidence in the macitentan DB treatment group (e.g., ATC and PT within each ATC with the highest number of occurrences appear first). Equal frequency of different ATC/PTs is sorted in alphabetical order of the ATC/PT.

Subjects who took the same therapy more than once (as qualified by the same PT) are counted only once.

Previous therapies are similarly summarized.

In addition to tabulations, study-concomitant therapies and previous therapies (including hormonal contraceptives, for females of childbearing potential only) are reported in a subject listing. Previous and study concomitant therapies are flagged accordingly.

10.4.5 Other subject characteristics

Other subject characteristics are summarized on the All-enrolled set.

10.4.5.1 Contraceptive methods

For females of childbearing potential only, contraceptive methods [as defined in Section 5.2.5.1] together with serum pregnancy tests data (i.e., choriogonadotropin beta) are presented in separate subject listings.

10.5 Analysis of study treatment exposure and compliance

Exposure data as well as drug accountability are provided in subject listings.

10.5.1 Exposure

Duration of exposure over the combined DB + OL period will be summarized using the All-treated DB + OL set.

Duration of exposure over the OL only period will be summarized using the All-enrolled set.

The duration of study treatment (irrespective of any treatment interruptions, see definition in Section 5.3.1) as well as the study treatment exposure (excluding interruptions see definition in Section 5.3.4) is summarized using descriptive statistics by DB treatment group. The study treatment duration is also summarized as a categorical variable, presenting the cumulative distribution of treatment duration by class interval (i.e., at least

4 weeks, at least 8 weeks, at least 12 weeks, at least 16 weeks, and every 4 weeks thereafter) and displaying counts and percentages of subjects in each class interval.

10.5.2 Compliance with study treatment

Compliance in combined DB + OL period will be summarized on the All-treated DB + OL set.

Compliance in OL period will be summarized on the All-enrolled set.

Compliance [see definition in Section 5.3.2] with study treatment for the Combined DB + OL period and for OL only period is summarized overall and by DB treatment group.

The counts and percentages of subjects with compliance < 80% and > 120% will be displayed.

10.5.3 Study treatment discontinuation

A summary table is provided for display, for each DB treatment group, and overall:

- Counts and percentages of subjects who prematurely discontinued study treatment [see definition in Section 5.3.3].
- Reason associated with study treatment discontinuation [see definition in Section 5.3.3].

Only the study treatment discontinuations during OL are included.

10.5.4 Study treatment adjustments and interruptions

The analysis of study treatment exposure, excluding interruptions is covered in Section 10.5.1 above.

10.6 Analysis of efficacy variables

No primary efficacy variables are described in this study. All efficacy analyses are considered exploratory. No hypothesis test comparisons will be made between the treatment groups. All efficacy endpoints are evaluated on the all-enrolled set.

- All efficacy endpoints are evaluated over the combined DB + OL period, using the DB baseline.

All results collected for 6MWD, WHO functional class, Borg dyspnea index and SpO_2, including those from unscheduled visits, are reported in a subject listing. Imputed values are flagged with their corresponding reason for imputation.

10.6.1 Efficacy variable: 6MWD

Descriptive statistics are presented for 6MWD by DB treatment group and overall (as applicable), for the following values:

- Observed value at baseline
- Observed value at each scheduled post-baseline Visit X
- Absolute change from baseline to Visit X.

A summary will be created for the combined DB + OL period. The summary will be repeated for the imputed values.

The following graphical displays for observed values will be created:

- Mean and 95% CLs for the change from DB baseline values for 6MWD over the combined DB + OL period (observed values);
- Mean and 95% CLs for the change from DB baseline values for 6MWD over the combined DB + OL period (imputed values).

10.6.1.1 Handling of missing data

Missing 6MWD values for assessments in the DB study are imputed as per the imputation mechanism described in the MAESTRO DB SAP [redacted].

In the DB study only three subjects had missing 6MWD values at Week 16, all in the macitentan treatment group. The reasons and with the imputed values were:

- 1 death (at 14.3 weeks), imputed with zero meters;
- 2 subjects with no assessment (1 subject discontinued study treatment on Day 12; 1 subject hospitalized after 10.6 weeks), imputed with ~0 meters.

Consequently, a simplified imputation mechanism is applied for missing values in the OL study. For missing 6MWD values in the OL study, the following imputation rules are applied:

- If the reason for missing data is death, a distance of zero (0) meters is imputed for all 6MWD visits from the date of death;
- For any other reasons, the last available value is carried forward.

10.6.2 Efficacy variable: WHO functional class

WHO functional class is summarized in shift tables by DB treatment group displaying:

- Counts of subjects in each category at baseline;

- Counts and percentages of subjects in each category at each scheduled post-baseline Visit X by category at baseline;
- Counts and percentages of subjects with improvement (i.e., shifted to a lower class), worsening (i.e., shifted to a higher class), and no change at Visit X together with the 95% confidence limits.

Summary will be created for the combined DB + OL period.

10.6.2.1 Handling of missing data

Missing WHO functional class values for assessments in the DB study are imputed as per the imputation mechanism described in the MAESTRO DB SAP [redacted]

For missing WHO functional class values in the OL study, the following imputation rules are applied:

- If the reason for missing data is death, class IV is imputed for all WHO visits from the date of death;
- For any other reasons, the last available value is carried forward.

10.6.3 Efficacy variable: Borg dyspnea index

Descriptive statistics are presented for Borg dyspnea index by DB treatment group, for the following values:

- Observed value at baseline
- Observed value at each scheduled post-baseline Visit X
- Absolute change from baseline to Visit X.

Summary will be created for the combined DB + OL period.

10.6.3.1 Handling of missing data

Missing Borg dyspnea index values for assessments in the DB study are imputed as per the imputation mechanism described in the MAESTRO DB SAP [redacted]

For missing Borg dyspnea index values in the OL study, the following imputation rules are applied:

- If the reason for missing data is death, a value of 10 is imputed for all Borg visits from the date of death;
- For any other reasons, the last available value is carried forward.

10.6.4 Efficacy variable: SpO_2

Descriptive statistics are presented for SpO_2 index by DB treatment group, for the following values:

- Observed value at baseline
- Observed value at each scheduled post-baseline Visit X
- Absolute change from baseline to Visit X.

At each post-baseline timepoint, only subjects who had both the assessment at baseline and the post-baseline visit are included. Separate summaries will be created for the combined DB + OL period.

10.6.4.1 Handling of missing data

No imputation of missing data for SpO_2 will be applied.

10.6.5 Supportive/sensitivity analyses

Not applicable.

10.6.6 Subgroup analyses

Not applicable.

10.7 Analysis of safety variables

All safety analyses will be performed on the Combined DB + OL period, using the all-DB + OL treated set.

10.7.1 Adverse events

All AEs captured are reported in the subject listing together with the assigned PT / system organ class (SOC). Treatment-emergent AEs [see definition in Section 5.6.1.1] are flagged accordingly.

A summary table with an overview of treatment-emergent AEs is provided by DB treatment group, displaying counts and percentages of subjects having experienced at least one treatment-emergent AE, severe AE, study-treatment related AE, AE leading to study treatment discontinuation, SAE, study-treatment related SAE, and fatal SAE.

Treatment-emergent AEs are summarized by DB treatment group displaying counts and percentages of subjects having experienced at least one treatment-emergent AE, together with counts and percentages one together with corresponding counts by SOC and by PT within each SOC. The summary tables are presented in descending order according to the DB-Macitentan incidence (e.g., SOC and PT within each SOC with the highest number of occurrences appears first). Equal frequency of different SOC/PTs is sorted in alphabetical order of the SOC/PT.

Treatment-emergent AEs related to study treatment are summarized similarly. Treatment-emergent AEs by maximum intensity are summarized similarly by PT, only.

10.7.2 Deaths, other serious adverse events

10.7.2.1 Death

All death cases are reported in the subject listing. Treatment-emergent deaths [see definition in Section 5.6.2] are flagged accordingly.

Counts and percentages of subjects who died (i.e., all deaths) are presented by PT (associated with the cause of death). The summary table is presented in descending order according to the DB-Macitentan incidence (e.g., PTs with the highest number of occurrences appears first). Equal frequency of different PTs is sorted in alphabetical order.

10.7.2.2 SAEs

All SAEs are reported in the subject listing. Treatment-emergent SAEs are flagged accordingly. All SAEs leading to hospitalization are reported in a separate subject listing with start date of admission and end date of discharge.

Treatment-emergent SAEs are summarized similarly to treatment-emergent AEs [see Section 10.7.1, by SOC and PT within each SOC as well as by PT].

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and not for the purpose of the clinical study report), separate similar summary tables are provided by SOC and PT within each SOC for:

- Treatment-emergent SAEs related to study treatment
- Treatment-emergent SAEs with fatal outcome
- Treatment-emergent SAEs related to study treatment with fatal outcome.

In addition, for the disclosure of the results to EudraCT and ClinicalTrials.gov, treatment-emergent SAEs are summarized displaying counts and percentages of subjects with at least one treatment-emergent SAE in the OL study plus the number of events (counted exactly the number of times they occurred also within a subject) by SOC and PT. The summary table is presented in descending order (i.e., SOC and PT within each SOC with the highest number of occurrences appears first). Equal frequency of different PTs is sorted in alphabetical order of the PT.

10.7.2.3 AEs leading to premature discontinuation of study treatment

A separate subject listing is provided with all AEs leading to premature discontinuation of study treatment.

AEs leading to premature discontinuation of study treatment are summarized similarly to treatment-emergent AEs [see Section 10.7.1, by SOC and PT within each SOC as well as by PT].

10.7.2.4 Other significant AEs

Treatment-emergent AEs with fatal outcome [see definition in Section 5.6.5.1] are summarized similarly to treatment-emergent AEs [see Section 10.7.1, by SOC and PT within each SOC as well as by PT].

For each area of clinical interest, treatment-emergent AESIs [see definition in Section 5.6.5.2] are summarized displaying counts and percentages of subjects having experienced at least one treatment-emergent AESI. Counts and percentages of subjects having experienced at least one treatment-emergent AESI are presented by frequency of PT within each SOC. Separate subject listings are provided with all AEs for the area of clinical interest.

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and not for the purpose of the clinical study report), treatment-emergent non-serious AEs [see definition in Section 5.6.5.3] with frequencies ≥ 5% are summarized displaying counts and percentages of subjects with at least a treatment-emergent non-serious frequent AE plus the number of events (counted exactly the number of times they occurred also within a subject) by SOC and PT. The summary table is presented in descending order according to the number of events (i.e., SOC and PT within each SOC with the highest number of occurrences appears first). Equal frequency of individual PTs is sorted in alphabetical order of the individual PT.

10.7.3 Electrocardiography

Not applicable.

10.7.4 Laboratory tests

All hematology and chemistry parameters [see Section 5.6.8] provided by the central and local laboratory are displayed in subject listings, including those from unscheduled visits. MLAs are flagged accordingly.

For each post-baseline visit (i.e., Visit 3/Week 4, Visit 4/Week 8, Visit 5/Week 12, Visit 6/Week 16/EOT in the DB study, and Visit 2/Month 1, each 6-monthly visit, and EOT in the OL study) laboratory test parameters (excluding serum pregnancy tests) are summarized, by DB treatment group, displaying descriptive statistics for:

- Observed value at baseline, at Visit X
- Absolute change from baseline to Visit X

Each evaluation includes only subjects who had both the assessments at baseline and the considered post-baseline visit. Similarly, laboratory test parameters (excluding serum pregnancy tests) are summarized, by DB treatment group, displaying descriptive statistics for:

- Observed value at baseline, up to 30 days after study treatment discontinuation
- Absolute change from baseline up to 30 days after study treatment discontinuation

In this evaluation, values from unscheduled visits are included.

Separate summaries are presented for hematology and clinical chemistry laboratory tests.

10.7.4.1 MLAs

For the evaluation of MLAs, values from unscheduled visits are included. Separate summaries are presented for hematology and clinical chemistry laboratory tests.

A dictionary listing of definitions of MLA (LL, LLL, HH, HHH) is provided for each parameter.

For each category (i.e., LL, LLL, HH, HHH, HHHH), treatment-emergent MLAs [see definition in Section 5.6.8.1] are summarized by DB treatment group, displaying counts and percentages of subjects with at least one treatment-emergent MLA for each parameter for which the marked abnormality is defined. Percentages are calculated as number of subjects with experiencing the abnormality for the parameter under consideration at least once, divided by the number of subjects with any post-baseline laboratory measurement (and for hemoglobin and creatinine, also with a valid baseline value based on the definition of the abnormality).

10.7.5 Vital signs and body weight

Body weight values [see definition in Section 5.6.6] including those from unscheduled visits are reported in a subject listing. BP measurements are reported in a separate subject listing.

For each post-baseline visit (i.e., Visit 3/Week 4, Visit 4/Week 8, Visit 5/Week 12, Visit 6/Week 16/EOT in the DB study, and Visit 2/Month 1, each 6-monthly visit, and EOT in the OL study) SBP, DBP, PR are summarized, by DB treatment group, displaying descriptive statistics for:

- Observed value at baseline, at Visit X
- Absolute change from baseline to Visit X.

In each evaluation, are included only subjects who had both the assessments at baseline and the considered post-baseline visit.

Similarly, SBP, DBP, PR, and body weight are summarized, by DB treatment group, displaying descriptive statistics for:

- Observed value at baseline, up to 30 days after study treatment discontinuation
- Absolute change from baseline up to 30 days after study treatment discontinuation.

In this evaluation, values from unscheduled visits are considered.

10.7.6 Other safety variables

10.7.6.1 Physical examination

Physical examinations [as defined in Section 5.6.9.1] performed during the course of the study are reported in a subject listing.

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 OL enrollment date

Date of OL enrollment collected in the "Enrollment" eCRF module.

11.2 End-of-Study date

Date of EOS visit collected in the "End of Study" eCRF module.

11.3 Study treatment start date

11.3.1 DB treatment start date

The study treatment start date in the DB study.

11.3.2 OL treatment start date

It is the first day of intake of study treatment during OL study. It is derived as the first treatment start date (in chronological order) in the "Exposure" eCRF module.

For analyses on the OL-only period the OL treatment start date is used as the "Study treatment start date"

11.3.3 Macitentan treatment start date

The date of first drug intake of macitentan. For subjects who received macitentan during the DB study, it is the study treatment start date of DB study as defined in Section 11.3.1, otherwise it is the study treatment start date of this OL study as defined in Section 11.3.2.

For analyses on the combined DB + OL period, the Macitentan treatment start date is used as the "Study treatment start date".

11.4 Study treatment end date/study treatment discontinuation (EOT)

11.4.1 DB treatment end date

It is the study treatment end date in the DB study.

11.4.2 OL treatment end date

It is the last day of intake of study treatment during OL study. It is derived as the last treatment end date (in chronological order) in the "Exposure" eCRF module.

For analyses on the OL only period the OL treatment end date is used as the "Study treatment end date/study treatment discontinuation (EOT)".

11.4.3 Macitentan treatment end date

It is the last drug intake of macitentan. For subjects who did not enter the OL study this is the study treatment end date of DB study as defined in Section 11.4.1, otherwise it is the study treatment end date (EOT) as defined in Section 11.4.2.

For analyses on the combined DB + OL period, the Macitentan treatment end date is used as the "Study treatment end date/study treatment discontinuation (EOT)".

11.5 Period

11.5.1 DB period

The DB period is the period from DB treatment start date [see Section11.3.1] to DB treatment end date [see Section 11.4.1].

11.5.2 OL period

The OL period is the period from OL treatment start date [see Section11.3.1] to OL treatment end date [see Section 11.4.1].

11.5.3 DB + OL period

The DB + OL period is the period from macitentan start date (see Section11.3.1) to macitentan treatment end date [see Section 11.4.1].

11.6 Study Day (Day)

11.6.1 OL study day

'OL study day' refers to the number of days elapsed since OL study treatment start date [Section 11.3.2] plus 1 (e.g., Day 1 is the day of study treatment start date). For dates prior to study treatment start date, study day is the negative number of days elapsed between the date under consideration and the day of study treatment start date. Therefore, the study day is always different from 0.

11.6.2 DB study day

'DB study day' refers to the number of days elapsed since DB study treatment start date [Section 11.3.2] plus 1 (e.g., Day 1 is the day of study treatment start date). For dates prior to study treatment start date, study day is the negative number of days elapsed between the date under consideration and the day of study treatment start date. Therefore, the study day is always different from 0.

11.7 Baseline

Except where otherwise specified, the baseline for a given measurement is the last value assessed ≤ the start date of study treatment defined in Section 11.3. If unscheduled/re-test visits are performed on the same day as treatment start, the available value from this test is considered for baseline.

The DB baseline is defined as the last value assessed ≤ the DB treatment start date defined in Section 11.3.1.

The OL baseline is defined as the last value assessed ≤ the OL treatment start date defined in Section 11.3.3.

The macitentan baseline is defined as the last value assessed ≤ the macitentan treatment start date defined in Section 11.3.3.

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

Incomplete or missing dates/times are handled as follows for the purpose of the analysis.

If the month is missing, then the day is also considered missing (if present).

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 of different dates refer to the first or last date, respectively, when ordered in sequence.

Data from the AC-055-305/MAESTRO study are taken from the analysis database using the imputation rules applied in AC-055-305/MAESTRO study; thus this section refers only to SDTM collected for the AC-055-308/MAESTRO-OL study.

Type of date/time	Date/time is incomplete	Date/time is missing
AE resolution date	The upper limit	No approximation, the AE is considered as ongoing in the analysis
AE onset date	If the end date of the AE is not before the start of study treatment OL, and if the study treatment start OL falls in the range of possible dates, it is the study treatment start date OL. In all the other cases, it is the lower limit	The earlier of the resolution of the AE and the study treatment start date
Concomitant therapy start date	If the end date of the therapy is not before the start of study treatment OL and the start of study treatment date OL falls in the range of possible dates, the start of study treatment date OL is used. In all other cases, it is the lower limit	No replacement, the therapy is considered as study /study treatment-concomitant if the end date is on or after the study treatment start date OL.
Concomitant therapy end date	The upper limit	No replacement (considered as ongoing)

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

This section lists all outputs (i.e., tables, listings, and figures) produced to report the results of the analyses defined in the sections above.

The table, listing and figures naming conventions have three components: ***Type*** (T, L, F), ***Name*** (free text, not longer than eight characters), ***Suffix*** (for example, for analysis sets, or subgroups, not longer than four characters). Multiple suffixes can be added; components/suffixes are separated by '_'.

Whenever possible, naming conventions and mock layouts are according to the BST Standard Outputs, version 3.0 as of 31 March 2016. Mock layouts are displayed in a separate document (Layouts for Tables Listings Figures [TLFs] of study AC-055-308/MAESTRO-OL).

Key deliverables are marked as a priority.

13.1 Subject disposition

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
ENRCS	T	Enrolled subjects by country and by site	ENR	✓	TS1
DISP	T	Disposition of subjects	ENR	✓	TS2
ANSETOV	T	Overview of analysis sets	TTS	✓	TS3
ANSET	L	Listing of subject participation in the different analysis sets	TTS		LS1

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.2 Protocol deviations

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PRDEVA	T	All protocol deviations	ENR		TS4
PRDEVI	T	Important protocol deviations	ENR	✓	TS4
PRDEV	L	Listing of protocol deviations	ENR		LS2

* T = Summary table, L = Listing, **ENR = All-enrolled set.

13.3 Subject characteristics

13.3.1 Demographics

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DEMOG	T	Demographic characteristics	ENR	✓	TS5
AGECATEU	T	EudraCT age categories	ENR		TS6

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DEMOG	L	Listing of demographic characteristics	ENR		LS3

* T = Summary table, L = Listing, **ENR = All-enrolled set.

13.3.2 Baseline disease characteristics

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
BLDISCHR	T	Baseline disease characteristics of subjects who entered the open-label study	ENR	✓	TS7
BASDC	L	Listing of baseline disease characteristics	ENR		LS4

* T = Summary table, L= Listing, **ENR = All-enrolled set.

13.3.3 Medical history

Not applicable.

13.3.4 Previous and concomitant therapies

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
CTSATCPR	T	Study-concomitant therapies by anatomical therapeutic chemical (ATC) class and preferred term	ENR		TS8
CTSPR	T	Study-Concomitant therapies by preferred term	ENR		TS9

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PCTHER	L	Listing of subjects with previous and study-concomitant therapies including hormonal contraceptives (for females of childbearing potential only)	ENR		LS5

* T = Summary table, L = Listing, ** ENR = All-enrolled set..

13.3.5 Specific previous and concomitant therapies

Not applicable.

13.3.6 Other subject characteristics

13.3.6.1 Contraceptive methods

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PREGN	L	Listing of childbearing potential and contraception	ENR		LS6
PREGN_SERUM	L	Listing of serum pregnancy data	ENR		LS7

* L = Listing, **ENR = All-enrolled set.

13.4 Study treatment exposure and compliance

13.4.1 Exposure

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
TREXP	T	Study treatment exposure combined DB+OL	TTS	✓	TS10
TREXP_OL	T	Study treatment exposure OL	ENR	✓	TS10
TREXP	L	Listing of exposure	TTS		LS8

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.4.2 Compliance with study treatment

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
COMPA	T	Compliance combined DB+OL	TTS		TS11
COMPA_OL	T	Compliance OL	ENR		TS11
COMPA	L	Listing of compliance	TTS		LS9

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.4.3 Study treatment discontinuation

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PDISCTR	T	Reasons for premature discontinuation of study treatment	ENR	✓	TS12

* T = Summary table, **ENR = All-enrolled set.

13.4.4 Study treatment adjustment/interruptions

Not applicable.

13.5 Study discontinuation

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PDISCST	T	Reasons for premature study discontinuation	ENR	✓	TS13
PDISC	L	Listing of discontinued subjects	ENR		LS10

* T = Summary table, L = Listing, ** ENR = All-enrolled set,

13.6 Efficacy analyses

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
6MWDDBOL	T	Absolute values and change from DB baseline for 6MWD - combined DB + OL period	ENR	✓	TS14
6MWDDBOL	F	Mean (95% CL) for change from DB baseline in 6MWD - combined DB + OL period (observed values)	ENR		FS1
6MWDIDBOL	F	Mean (95% CL) for change from DB baseline in 6MWD - combined DB + OL period (imputed values)	ENR		FS1
WHODBOL	T	Shift table from baseline to post-baseline visits in WHO functional class - combined DB + OL period	ENR	✓	TS15
BORGDBOL	T	Absolute values and change from DB baseline for Borg dyspnea index - combined DB + OL period	ENR	✓	TS14
SPO2DBOL	T	Absolute values and change from DB baseline for SpO2 - combined DB + OL period	ENR	✓	TS14
EFF	L	Listing of all efficacy data	ENR		LS11

* T = Summary table, L = Listing, F = Figure, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7 Safety analyses

13.7.1 Adverse events

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEOV	T	Overview of treatment-emergent adverse events (AE)	TTS	✓	TS16
AESCPR	T	Treatment-Emergent adverse events (AE) by system organ class and preferred term	TTS		TS17
AEPR	T	Treatment-Emergent adverse events (AE) by preferred term	TTS	✓	TS18
AEPRIN	T	Treatment-Emergent adverse events (AE) by maximum intensity	TTS		TS19
AERESCPR	T	Treatment-Emergent adverse events (AE) related to study treatment by system organ class (SOC) and preferred term	TTS		TS17
AEREPR	T	Treatment-Emergent adverse events (AE) related to study treatment by preferred term	TTS		TS18
AE	L	Listing of adverse events (AE)	TTS		LS12

* T = Summary table, L = Listing, F = Figure, , **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7.2 Deaths

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DEAPR	T	Cause of death	TTS	✓	TS20
DEATH	L	Listing of deaths	TTS		LS14

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7.3 Serious adverse events

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SAESCPR	T	Treatment-Emergent serious adverse events (SAE) by system organ class (SOC) and preferred term	TTS	✓	TS17
SAEPR	T	Treatment-Emergent serious adverse events (SAE) by preferred term	TTS		TS18
SAERESCPR	T	Treatment-Emergent serious adverse events (SAE) related to study treatment by system organ class (SOC) and preferred term	TTS		TS17
SAEFASCPR	T	Treatment-Emergent serious adverse events (SAE) with fatal outcome by system organ class (SOC) and preferred term	TTS		TS17
SAERFSCPR	T	Treatment-Emergent serious adverse events (SAE) related to study treatment with fatal outcome by system organ class (SOC) and preferred term	TTS		TS17
SAESCPRE	T	Occurrence of treatment-emergent serious adverse events (SAE)	ENR		TS21

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SAE	L	Listing of serious adverse events (SAE)	TTS		LS12
SAEHOSP	L	Listing of serious adverse events (SAE) leading to hospitalization	TTS		LS13

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7.4 Adverse events leading to premature discontinuation of study treatment

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEPDSCPR	T	Adverse events (AE) leading to premature discontinuation of study treatment by system organ class (SOC) and preferred term	TTS	✓	TS17
AEPDPR	T	Adverse events (AE) leading to premature discontinuation of study treatment by preferred term	TTS		TS18
AEPD	L	Listing of adverse events (AE) leading to premature discontinuation of study treatment	TTS		LS12

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7.5 Other significant adverse events

13.7.5.1 AEs with fatal outcome

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEFASCPR	T	Treatment-Emergent adverse events (AE) with fatal outcome by system organ class (SOC) and preferred term	TTS		TS17
AEFAPR	T	Treatment-Emergent adverse events (AE) with fatal outcome by preferred term	TTS		TS18

* T = Summary table, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7.5.2 AEs of special interest

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AESIPR_ANAE	T	Treatment-Emergent adverse events (AE) of special interest related to anaemia by preferred term	TTS		TS18
AESIPR_HYPO	T	Treatment-Emergent adverse events (AE) of special interest related to hypotension by preferred term	TTS		TS18
AESIPR_OEDE	T	Treatment-Emergent adverse events (AE) of special interest related to oedema and fluid overload	TTS		TS18
AESI_ANAE	L	Listing of adverse events (AE) of special interest related to anaemia	TTS		LS12

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AESI_HYPO	L	Listing of adverse events (AE) of special interest related to hypotension	TTS		LS12
AESI_OEDE	L	Listing of adverse events (AE) of special interest related to oedema and fluid overload	TTS		LS12

* T = Summary table, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.7.5.3 Non-serious AEs

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
NSAEFSCPRE	T	Occurrence of non-serious frequent treatment-emergent adverse events (AE)	ENR		TS21

* T = Summary table, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.8 Electrocardiogram

Not Applicable.

13.9 Laboratory tests

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABCGTPA_HEM	T	Hematology: change in laboratory tests from baseline up to 30 days after study treatment discontinuation	TTS		TS22
LABCGTPB_HEM	T	Hematology: change in laboratory tests from baseline to each scheduled post-baseline visit	TTS		TS22

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABCGTPA_CHE	T	Clinical chemistry: change in laboratory tests from baseline up to 30 days after study treatment discontinuation	TTS		TS22
LABCGTPB_CHE	T	Clinical chemistry: change in laboratory tests from baseline to each scheduled post-baseline visit	TTS		TS22
LABMLA_HEM	T	Hematology: treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation	TTS	✓	TS23
LABMLA_CHE	T	Clinical chemistry: treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation	TTS	✓	TS23
LABABLIV	T	Treatment-emergent elevated liver tests and additional hemoglobin laboratory abnormalities up to 30 days after study treatment discontinuation	TTS	✓	TS24
LAB	L	Listing of individual laboratory measurements (SI units)	TTS		LS15
LABORI	L	Listing of individual laboratory measurements (original units)	TTS		LS16

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABLMA_DEF	L	Listing of definitions of marked laboratory abnormality	Not applic-able		LS17
LABLMA	L	Listing of individual laboratory measurements, subjects with at least an additional liver or hemoglobin laboratory abnormality	TTS		LS15

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.10 Vital signs and body weight

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
VITCGTPA	T	Vital signs and body weight: change from baseline up to 30 days after study treatment discontinuation	TTS	✓	TS22
VITCGTPB	T	Vital signs and body weight: change from baseline to each scheduled post-baseline visit	TTS		TS22
VIT_BPM	L	Listing of vital signs: blood pressure measurements and body weight	TTS		LS18

* T = Summary table, L = Listing, **ENR = All-enrolled set, TTS =All-treated DB + OL set.

13.11 Other safety variables

13.11.1 Physical Examination

Output name	Display *	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PHYSF	L	Listing of physical findings	TTS		LS19

* L = Listing, ** TTS =All-treated DB + OL set.

14 REFERENCES

[D-14.170] AC-055-308 MAESTRO-OL: Long term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome. Actelion Pharmaceuticals Ltd; Global Protocol Version 4, 16 May 2014.

15 APPENDICES

Appendix A Document history

Version	Effective Date	Reason
1.0	*6-DEC-17*	New