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

Statistical Analysis Plan (SAP) for Clinical Study Report (CSR)

Long term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects within operable chronic thromboembolic pulmonary hypertension (CTEPH)
MERIT-2: Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension (Open-Label)

Protocol AC-055E202; Phase 2

JNJ-67896062 (Macitentan)

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	19 November 2021	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the methods, conduct and content of the statistical analyses of safety and exploratory efficacy data, for the purpose of the production of the Clinical Study Report (CSR) for the open-label (OL) extension study AC-055E202/MERIT-2, hereafter referred to as the OL study to the double-blind (DB) study AC-055E201/MERIT-1.

- AC-055E201(MERIT-1), was a prospective, randomized, placebo-controlled, DB, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable CTEPH (completed study).
- AC-055E202 (MERIT-2) is a long-term, multicenter, single-arm, OL extension study of the MERIT-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable CTEPH.

The purpose of this MERIT-2 study was to gather additional experience with macitentan 10 mg in subjects with inoperable CTEPH beyond the 24 weeks of treatment in the DB AC055E201 / MERIT-1 study. The rationale of this study relies on the fact that the long-term safety of macitentan in this population is not yet known. It is also unknown whether the treatment effect of macitentan (if any) reaches a plateau at 24 weeks (end of the DB study) or would still increase over a longer treatment period.

HGRAC [Human Genetic Resources Administration of China] approval is missing for MERIT-2 study; hence to ensure compliance with the data exporting rules under the HGRAC Regulation a cut-off date of 17 OCT 2019 will be applied for the data from Chinese sites in the clinical database. Any significant safety information including SAE, fatal events and pregnancy reported to the global safety database after 17Oct19 will be included in the CSR. The data from all other sites will be included up to study lock.

This SAP also provides a description of the general considerations and assumptions for the pooled data of AC-055E201/MERIT-1 (DB) and AC-055E202/MERIT-2 (OL). The purpose of pooling the data from MERIT-1 and MERIT-2 studies is to provide long-term follow-up data, in subjects with inoperable CTEPH who were exposed to macitentan in the DB phase and/or in the OL extension phase.

The pooling of MERIT-1 and MERIT-2 means that the data from the same subjects randomized in MERIT-1 will be concatenated with their data from the OL extension study (MERIT-2). The concatenation of data from the same subjects is referred to as 'pooling' in this document.

This SAP refers to the documents listed in Table 2.

Table 2 – Study Documents

Document	Date, Version
Protocol AC-055E202	V4, 22 June 2021
SDTM annotated CRF Draft	V1.6, 11 Mar 2021 1
SAP for CSR AC-055E201	V. 1.0, 27 Sep 2016
sNDA SAP	V. 3, 3 Apr 2018

2. OBJECTIVES

2.1. Safety Objective

To evaluate the long-term safety and tolerability of macitentan 10 mg in subjects with inoperable CTEPH.

2.2. Efficacy Objectives

To evaluate the long-term effects of macitentan 10 mg on exercise capacity and functional class (FC).

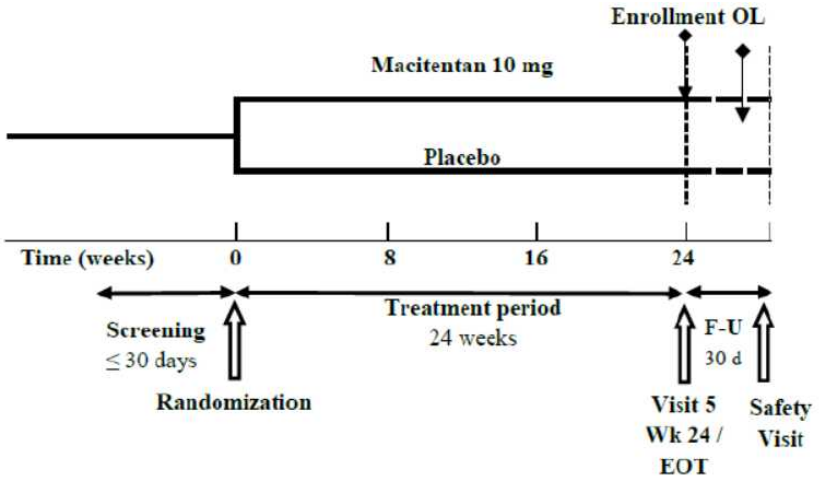
3. STUDY DESIGN

3.1. AC-055E201(MERIT-1)

A total of 80 subjects with inoperable CTEPH in World Health Organization Functional Class (WHO FC) II–IV with a pulmonary vascular resistance (PVR) ≥ 400 dyn·sec/cm−5 and 6-minute walk distance (6MWD) ≥ 150 m and ≤ 450 m were randomized 1:1 to macitentan or placebo and received double blind treatment for 24 weeks. Treatment with phosphodiesterase type-5 inhibitors (PDE-5i) or oral/inhaled prostanoids was allowed for subjects in WHO FC III-IV, but not for subjects in WHO FC II.

In MERIT-1 (Figure 1), the safety follow-up period was up to EOT + 30 days, or up to the start of MERIT-2 OL treatment (whichever occurred first).

Figure 1 – AC-055E201 (MERIT-1) DB study design



Source: AC-055E201 (MERIT-1) Clinical Study Report, Figure 9-1.
EOT = End-of-Treatment; F-U = follow-up; OL = open-label; PTOP = post-treatment observational period.

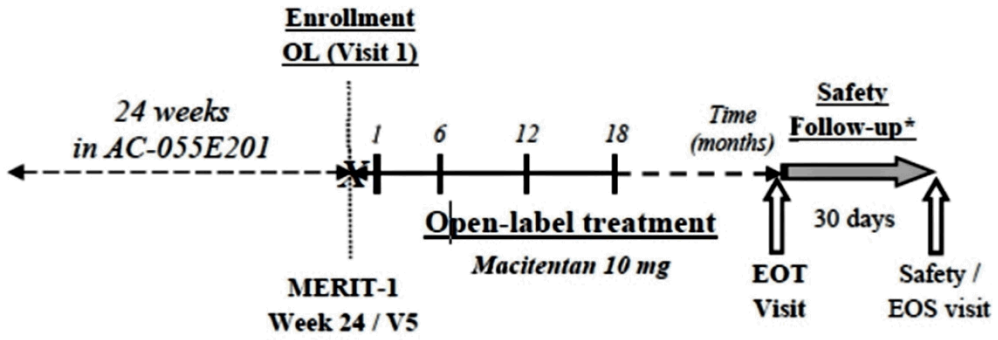
3.2. AC-055E202 (MERIT-2).

In total, 76 subjects (males or females) who remained in the DB AC-055E201 / MERIT-1 study up to Week 24 (see Table 5), irrespective of premature discontinuation of study treatment (except if discontinuation was due to a hepatic AE or liver aminotransferase abnormalities) were eligible to enter this OL extension study and were treated with macitentan 10 mg. The investigators and

subjects did not know the treatment assignment in MERIT-1 (macitentan 10 mg or placebo) at the time of inclusion into MERIT-2. The study is conducted in 4 geographical regions (15 countries and 35 activated sites)). Site in Switzerland was initiated and then closed as the subjects did not roll over.

A post-treatment safety follow-up period (30 days) follows the permanent study drug discontinuation.

Figure 2 – AC-055E202 (MERIT-2) OL study design



EOS = End-of-Study; EOT = End-of-Treatment; OL = open-label.
*For subjects who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (EOS, which corresponds to EOT visit in this case).

3.3. Study periods

The MERIT-2 OL study comprises the following consecutive periods:

3.3.1. Treatment Period

For each subject, the OL treatment duration will last from his/her enrollment (Visit 1) up to the End-of-Treatment, i.e., until whichever of the following occurs first:

- Commercial availability of macitentan in this indication in the subject's country
- Sponsor decides to stop this study (AC-055E202 / MERIT-2 OL extension)
- The subject or the investigator decides to discontinue the study drug.

After the Enrollment visit, subjects were to come to the site at Month 1 (Visit 2), Month 6 (Visit 3), and every 6 months thereafter (Visits 4, 5, 6…), up to the EOT visit (see Figure 2). In addition, subjects will perform monthly laboratory and safety monitoring (see Table 3).

3.3.2. Safety Follow-up Period

For each subject, a post-treatment Safety follow-up period (30 days) will follow the permanent study drug discontinuation. For subjects who are entering a continued access program, the enrollment into the continued access program (post-trial access program or other open-label study) must occur on the day of the last visit of the MERIT-2 study (EOS, which corresponds to EOT visit in this case), see Figure 2.

3.3.3. Unscheduled Visits

Unscheduled visits may also take place anytime during the study. These visits include (but are not limited to) those performed due to safety (e.g., occurrence of an adverse event, laboratory abnormalities) and/or CTEPH related (e.g., disease progression) issues.

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits are recorded in the 'Unscheduled visit - Reason' CRF form. Any of the analyzed laboratory parameters listed in Section 7.3.4.3 of the Protocol, should be analyzed at the central laboratory (except in case of emergency). The results done at a local laboratory, are checked as 'Yes' in the 'Local lab summary' CRF form (see Section 7.3.4.2 of the Protocol).

Table 3 – Visit and Assessment Schedule

PERIODS	Name	TREATMENT						FOLLOW-UP
	Duration	Open						30 days
VISITS	Number	1	2	Monthly lab. & Safety Monitoring[j]	3, 4, 5….		Ul, 2, 3…	
	Name	Enrollment[d]	Month 1		Month 6, Month 12, Month 18…	End-of-Treatment	Unscheduled	Safety Follow-up / EOS[k]
	Time	Day 1	Month 1 (± 1 week)	Month 2 & every month thereafter (± 1 week)	Month 6 & every 6 months thereafter (± 2 weeks)	Within 7d after study drug disc.	Any time[f]	30-33 days after study drug disc.
Informed consent		X						
Concomitant medications		X	X	X	X	X	X	X
Physical examination		X	X		X	X	X	X
Vital signs (BP – HR), weight		X	X		X	X	X	X
WHO FC/6MWT/Borg dyspnea index		X			X	X	X	
Complete laboratory tests[a]		X[b]	X		X	X	X	X
LTs				X				
Hemoglobin[c]				X				
Serum pregnancy test[e]		X	X	X	X	X	X	X
Study drug dispensing/return[g]		X	X	X	X	X	X	
AEs[h]		X	X	X	X	X	X	X
SAEs[i]		X	X	X	X	X	X	X

6MWT = 6-minute walk test; AEs = adverse events; BP = blood pressure; EOS = End-of-Study; FC = functional class; HR = heart rate; LTs = liver tests; SAEs = serious adverse events.

a. Complete laboratory tests: hematology and blood chemistry. All blood samples will be sent to the central laboratory for analysis.
b. 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.
c. Hemoglobin concentration will be measured every month during the first 6 months, and every 3 months thereafter up to the EOT visit.
d. For subjects who remain in the DB MERIT-1 study up to Week 24, the Enrollment visit is combined with the MERIT-1 Visit 5 / Week 24. Tests are not to be repeated if performed for the MERIT-1 Visit 5 / Week 24 on the day of this Enrollment visit.
e. Females of childbearing potential only.
f. Unscheduled visits can be performed at any time during the study, according to investigator's discretion. Any study specific procedure/assessment can be performed at an unscheduled visit; corresponding data will be collected in the electronic case report form.
g. Study drug dispensing according to investigational site practice (e.g., every 6 months, or every month).
h. AE reporting: all AEs occurring from study drug initiation and up to 30 days after study drug discontinuation.
i. SAE reporting: all SAEs occurring from signature of informed consent and up to 30 days after study drug discontinuation.
j. If the monthly laboratory samples are not collected at the site, the safety monitoring (assessments of AEs, SAEs, concomitant medications and methods of contraception) should be done via a telephone call that must be documented in the subject's file.
k. For participants who transition to a continued access program (post-trial access program or other open-label extension study), the EOT visit is defined as the EOS.

3.4. Data Displays and Cohorts

For the statistical analyses, following cohorts were defined in this SAP (see Table 5) in accordance with the analysis sets defined in the Protocol (see Section 5 of this SAP and Section 11.2 of the Protocol).

Table 4 – Cohorts vs Analysis sets

Cohorts defined in this document	Analysis sets defined in MERIT-2 protocol
Macitentan 10 mg MERIT (DB/OL)	Restricted Analysis set (RAS)
Macitentan 10 mg MERIT-2 (OL)	Open-Label Analysis Set (OLAS)
Macitentan 10 mg Pool	Open-Label Safety Set (OLSS)

DB = double-blind, OL = open-label

Analyses will be provided for the following cohorts:

- **Macitentan 10 mg MERIT (DB/OL)** (N = 40): All subjects randomized to macitentan 10 mg in MERIT-1 DB and who received at least one dose of macitentan in MERIT-2. This cohort is not subject to any cross-over effect of treatment and includes subjects who received macitentan in MERIT-1 and MERIT-2 (see Table 5).
- **Macitentan 10 mg MERIT-2 (OL)** (N = 76): All subjects enrolled in MERIT-2 and treated with macitentan 10 mg in MERIT-2 OL (regardless of randomized treatment in MERIT-1 DB). This is MERIT-2 OL analyses population (see Table 5).
- **Macitentan 10 mg Pool** (N = 76): All subjects treated with macitentan in MERIT-1 DB and/or the MERIT-2 OL extension study and subjects who received "any time macitentan".

Table 5 – Definition of Cohorts

Cohort	Population	Database		Reasons and additional comments
		From	Until	
Macitentan 10 mg MERIT (DB/OL) (N =40)	All subjects randomized to macitentan 10 mg in MERIT-1 DB and received at least one dose of macitentan 10 mg in MERIT-2 OL	Date of randomization (efficacy) / start of macitentan treatment (safety) in MERIT-1 DB study.	EOS for all subjects (except for Chinese subjects until 17 OCT 2019)	Long-term efficacy, safety and survival will be summarized for subjects who received macitentan 10mg in MERIT-1 DB and MERIT-2 OL (including data from MERIT-2 OL extension study). The time period is MERIT-1 and MERIT-2. For baseline definitions, see Section 8.3.
Macitentan 10 mg MERIT-2 (OL) (N =76) Previously on DB Macitentan 10 mg (n = 40) Previously on DB Placebo (n =36) All subjects (N = 76)	All subjects enrolled and treated with macitentan 10 mg in MERIT-2 OL	Start of macitentan treatment in MERIT-2 OL study	EOS for all subjects (except for Chinese subjects until 17 OCT 2019)	MERIT-2 safety and efficacy will be summarized. The time period is MERIT-2 only. The results in this cohort will be presented overall and by prior double-blind treatment in MERIT-1, i.e., placebo or macitentan 10 mg). For baseline definition, see Section 8.3.
Macitentan 10 mg Pool (N = 76)	All subjects treated with macitentan 10 mg in MERIT-1	Start of macitentan treatment in MERIT-1 DB	EOS all subjects (except for Chinese	Safety and survival will be summarized for subjects who received macitentan 10 mg anytime.

	DB and/or MERIT-2 OL	or MERIT-2 OL study	subjects until 17 OCT 2019)	For baseline definitions, see Section 8.3. Largest body of macitentan safety data based on cumulative exposure to macitentan from MERIT-1 and MERIT-2

4. STATISTICAL HYPOTHESES

As the primary objective of the study is long-term safety and all the efficacy analyses are considered exploratory, no formal hypothesis testing will be performed.

4.1. Sample Size Determination

No sample size calculation was done in the OL study, as subjects were not randomized. The number of subjects in the OL study was based on the number of subjects in the DB study that were eligible to transition to the OL study.

5. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Open-Label Analysis Set (OLAS)	The OL analysis set (OLAS), comprises all data from subjects who enrolled into the OL extension study, from the time they enter the OL extension study.
Restricted Analysis Set (RAS)	The restricted analysis set (RAS), comprises all data from subjects enrolled in the OL extension study who received macitentan 10 mg during the AC-055E201 / MERIT-1, from the time they enter the DB study.
Open-Label Safety Set (OLSS)	OL Safety Set (OLSS), comprises all DB and OL study subject data from subjects enrolled in OL extension study and who received macitentan 10 mg at least once, during either the DB or OL extension study for the period they are exposed to macitentan 10 mg.

5.1. Use of Analyses Sets

1. The analyses of the exploratory efficacy endpoints will be performed on the OLAS and RAS:

- On the OLAS, as change from baseline of the OL extension study, by randomized treatment group (see Section 3.4 and Table 8).
- On the RAS, as change from baseline of the DB core study in macitentan 10 mg only (see Section 3.4 and Table 8).

2. The analyses of the safety endpoints will be performed on the OLSS, OLAS and RAS:

- The OLSS, OLAS and RAS will be used for the analyses of the safety variables (see Section 3.4 and Table 9).
- The RAS and OLSS will be also used in estimation of overall survival.

Duration of treatment exposure will be evaluated on all analysis sets, OLAS, RAS and OLSS.

Listings will be prepared on the RAS, OLAS, and OLSS as appropriate.

Subject disposition will be summarized for the OLAS.

No per protocol analyses will be conducted.

Table 6 – Use of Analysis Sets for Analysis of Efficacy and Safety Variables

	Analysis Sets		
Variable	**OLAS**	**RAS**	**OLSS**
Efficacy			
6MWD	x	x	
Borg dyspnea index	x	x	
WHO FC	x	x	
Safety			
AEs*	x	x	x
SAEs	x	x	x
Deaths	x	x	x
Overall survival		x	x
Laboratory parameters and marked laboratory abnormalities	x	x	x
Vital Signs and body weight	x	x	x
Physical examination	x	x	x
Subject Disposition	x		
Demographics	x		
Exposure	x	x	x
Compliance	x		
Protocol Deviations	x		
Concomitant medications	x		

6MWD = 6-minute walk distance; *AEs = adverse events, including AESI, AEs leading to treatment discontinuation; SAE = serious adverse event, including SAEs with fatal outcome; FC = functional class; OLAS = Open-Label Analysis Set; OLSS = Open-Label Safety Set; RAS = Restricted Analysis Set; WHO = World Health Organization.

6. DEFINITION OF VARIABLES

The following dates will be used to define the treatment durations and safety reporting periods. For imputation of partial/ missing date, refer to Section 9.

The study end date (EOSDT2) for Chinese data will be associated with the cut-off date (CUTOFDT).

- Start date of treatment in MERIT-1 DB (TRTSDT1): Date of the start of treatment in MERIT-1 DB.
- End date of Treatment in MERIT-1 DB (TRTEDT1): Date of end of treatment in MERIT-1 DB.
- Start date of macitentan in MERIT-2 OL (TRTSDT2): Date of treatment start in MERIT-2 OL. This is the first treatment start date (in chronological order) recorded in the 'Study Drug Log' case report form (CRF).
- End date of macitentan in MERIT-2 OL (TRTEDT2): Date of end of treatment in MERIT-2 OL. This is the last treatment end date (in chronological order) recorded in the 'Study Drug Log' CRF. For subjects who are still ongoing (as long as there is no corresponding record in the Disposition [DS] domain), it will be assumed that they are still on-treatment at their last contact date (LCTDT202), and the end date of macitentan is the earliest of (last contact date, death date). For subjects entering a continued access program, the EOT visit is defined as the EOS visit.
- EOT: For subjects in all cohorts (see definitions in Table 5) this is TRTEDT2.
- Cut-off date (CUTOFDT): 17 October 2019 is the cut-off date to apply for the China's data collected in MERIT-2 OL. Except as otherwise specified, all data collected will be included in the analyses.
- Date of death (DTHDT): Actual date of death of a subject as reported in the 'Death Form' of the CRF, prior to the EOT+30 days, except where otherwise specified.
- MERIT-1 DB EOS date (EOSDT1): EOS visit date from the MERIT-1 DB study.
- MERIT-2 OL EOS date (EOSDT2): all enrolled subjects who received study drug must be followed up to the EOS, whether or not they are prematurely discontinued from study treatment.
- For an individual participant, EOS visit is defined as follows:
  - For participants that complete treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake.
  - For participants that prematurely discontinue study treatment, EOS visit is defined as the safety follow-up visit 30–35 days after last study treatment intake.
  - For participants who complete treatment and who are entering a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOT visit. For all subjects, the reason for premature discontinuation from study and the decision owner (as applicable) are documented in the 'Premature study discontinuation' eCRF form.
- MERIT-2 OL last contact date (LCTDT202): Last contact date is the date of the last visit, or, in case of lost to follow-up, the date of the last successful contact attempt (as reported in 'Lost to follow-up' form of the CRF) prior to the EOS. If any of the components (visit date or last successful contact attempt) is partial, the lower limit will be applied.

- OL study day: 'OL study day' refers to the number of days elapsed since OL study treatment start date (TRTSDT2) +1. For dates prior to study treatment start date, study day is the negative number of days elapsed between the date under consideration and the study treatment start date. Therefore, the study day is always different from 0.
- DB study day: 'DB study day' refers to the number of days elapsed since the day of randomization plus 1 (as randomization is considered Day 1). For dates prior to randomization, study day is the negative number of days between the date under consideration and randomization date. Therefore, the study day is always different from 0.

7. DISPOSITION

7.1. Disposition of Subjects

A study flowchart will be used to show the disposition of study subjects throughout the progression of the study. It will display the numbers of subjects randomized into the AC-055E201 / MERIT-1 study divided into the placebo and macitentan 10 mg treatment groups to which they were randomized. The number of subjects by treatment group entering into the AC-055E202 / MERIT-2 OL extension study along with the number of subjects continuing and discontinuing treatment and follow-up during the OL extension study, along with reasons for discontinuations will be displayed. The final row of the flowchart will result in the number of subjects completing the OL extension study in each DB treatment group of the Macitentan 10 mg OL cohort (see Section 3.4).

The items in the flowchart will be supported by tables and listings related to each level and will be presented on the OLAS (Macitentan 10 mg OL cohort, see Section 3.4):

- The number and percentage of subjects who completed the study treatment.
- The number and percentage of subjects who discontinued the study treatment early.
- The number and percentage of subjects who completed the study.
- The number and percentage of subjects who discontinued the study.
- Reasons for premature study treatment discontinuation.
- Reasons for premature study discontinuation.

Reasons for study drug discontinuation and reasons for study discontinuation will be retrieved from the 'Premature Permanent Discontinuation of Study Treatment' and 'Premature study discontinuation' CRF forms respectively.

The number and percent of subjects included and excluded from OLAS, based on the analysis set definitions in Section 5 will be summarized in tables and listings. Major protocol deviations will also be summarized in a table. (see Appendix 4). Major protocol deviations will be displayed by region, country, and site.

8. STATISTICAL ANALYSES

8.1. General Considerations

- Unblinding of study drug code occurred after AC-055E201 / MERIT-1 study database closure in accordance with sponsor standard operating procedures (SOPs).

- Analyses will be conducted only on data from subjects who enrolled in the OL study and were exposed to macitentan 10 mg at least once, during either the DB or OL extension studies.
- AEs will be coded using the latest version 24.1 of the MedDRA dictionary. Concomitant Medications (Appendix 5) will be coded using the same versions of the WHO drug code and the Anatomic Therapeutic Chemical class code dictionaries as used in the AC-055E201 / MERIT-1 study.
- All major protocol deviations (Appendix 4) related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment will be described in the final report. Subject listings for protocol deviations will be presented broken down by region, country and site.
- All analysis variables will be summarized and listed; variables to be presented in figures are specified in the corresponding Sections 8.5.2 and 8.6.2 of the SAP.
- Data will be listed and summarized by appropriate descriptive statistics (tables or figures), typically including:
  - Number of non-missing observations, number of missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous variables.
  - For time points where only one observation is available, the descriptive summary statistics will be provided with the NE (Not Evaluable) standard deviation (SD).
  - Number of events, number of censored observations, number of subjects at risk, and Kaplan-Meier estimates of the survival function for time-to-event variables.
  - Number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the sum of number of non-missing observations and total number of observations) for categorical variables.

Absolute changes from baseline are defined as: post-baseline value minus baseline value.

Study data tabulation model (SDTM) datasets of AC-055E202 / MERIT-2 study provided by Sponsor Clinical Development Data Management (CDDM) via the Life Science Analytics Framework (LSAF) system and Analysis Data Model (ADaM) datasets from AC-055E201 / MERIT-1, hereafter referred to as the double-blind (DB) study, are used as source data for the statistical analyses.

In the listings based on OLAS, only data split by groups 'Previously on DB Macitentan 10 mg' and 'Previously on DB Placebo' will be provided (not for All subjects).

All descriptive or formal statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise specified.

Major protocol deviations are defined as 'Important' in the eCRF.

8.2. Rules for Reporting Descriptive Statistics

There are three J&J standard alternatives, please refer to the table below, where X is the number of decimals in the SDTM:

	Default Conventions	Alternative 1	Alternative 2
Individual values	X	X	X
Mean	X+1	X+1	X
SD	X+2	X+1	X
Range (Min; Max)	X; X	X; X	X; X
Median	X+1	X+1	X
Q1; Q3	X+1; X+1	X+1; X+1	X; X

The following rules will be applied in reporting descriptive statistics:

- Always use the 'Default Conventions'.
- Use 'Alternative 2' only when is an issue for displaying statistics according to the layout (for example for laboratory when there are 3 decimals from SDTM).
- p values: please use 4 decimal places; if the p-value is less than 0.0001, the p-value has to be presented as <0.0001.

8.3. Definition of Baseline

The baseline for MERIT-1 safety and efficacy analysis is defined as:

- for the efficacy endpoints, the baseline value is the value from the last non-missing assessment obtained prior to, i.e., before or on the day of, randomization.
- For the safety and tolerability endpoints, the baseline value is the value from the last non-missing assessment obtained prior to, i.e., before or on the day of the start of study drug (CSR AC-055E201).

The MERIT-1 baseline will be used for summaries in 'Macitentan 10 mg MERIT (DB/OL)' cohort (see Section 3.4).

For the MERIT-2 summaries in cohort 'Macitentan 10 mg MERIT-2 (OL)' baseline value is the last non-missing assessment obtained prior to the start of macitentan in MERIT-2 OL.

For the 'Macitentan 10 mg Pool' cohort, baseline value is the last non-missing assessment obtained prior to the start of macitentan in MERIT-1 DB or MERIT-2 OL.

8.4. Visit Windows

To minimize missing data and to analyze the data at the relevant planned (scheduled) visits, all recorded assessments up to EOS are re-assigned to the most appropriate time point according to the best fitting time-window for that visit (see Table 7). Any unscheduled assessment (including endpoint variable, EOT and EOS assessments) will also be mapped to a time-window.

Should more than one assessment fall within the same time window, then the closest value to the planned time point will be assigned to the said time point for use in data summaries and analyses. In case of values that are equidistant to the planned time point, the last assessment will be considered for the analyses. If more than one value falls on the same day, then the worst value will be used (e.g. for 6MWD the smallest value will be used).

For 6MWD and Borg dyspnea index, the date of 6MWD will be used to perform the mapping. For WHO visits the 6MWD dates will be assigned as described in Section 8.5.2.

Table 7 – Visit Windows

Mapping Visits to:	Study Day* (nominal value)	Lower limit study day*	Upper limit study day	Period
MERIT-1				
Baseline		NA	1	Efficacy and Safety
Week 8	57	2	85	Efficacy and Safety
Week 16	113	86	141	Efficacy and Safety
Week 24	169	142	NA**	Efficacy and Safety
MERIT-2				
Baseline (Week 24 of MERIT-1)	-	NA	1	Efficacy and Safety
Month 6	180	2	270	Every 6 months Efficacy
Month 12	360	271	450	Every 6 months Efficacy
Month Y	Y*30	Y*30 -90+1	Y*30 +90	Every 6 months Efficacy
Month 1	30	2	45	Monthly Safety
Month 2	60	46	75	Monthly Safety
Month 3	90	76	105	Monthly Safety
Month 4	120	106	135	Monthly Safety
Month X	X*30	X*30 -15+1	X*30 +15	Monthly Safety
etc.	…	…	…	…
Month 1	30	2	105	Every 6 months Safety
Month 6	180	106	270	Every 6 months Safety
Month 12	360	271	450	Every 6 months Safety
Month Y	Y*30	Y*30 -90+1	Y*30 +90	Every 6 months Safety

*Study day in MERIT-1 or MERIT-2 are derived based on DB or OL treatment start date.**NA = not applicable as Week 24 was the end of MERIT-1

8.5. Efficacy

There are no primary or secondary efficacy variables defined for MERIT-2 OL; exploratory efficacy variables are described in protocol Section 11.1.2 and are presented below.

8.5.1. Definition of Exploratory Efficacy Variables

- Change from baseline to each scheduled time point in exercise capacity, as measured by the 6-minute walk distance (6MWD)
- Change from baseline to each scheduled time point in Borg dyspnea index collected at the end of the 6-minute walk test (6MWT)
- Proportion of subjects with worsening of WHO FC from baseline to each scheduled time point.

Table 8 – Efficacy Endpoints/Cohorts

	Macitentan 10 mg MERIT (DB/OL)	**MERIT-2 Macitentan 10 mg MERIT-2 (OL)**		
Efficacy Endpoint	(N=40)	Previously on DB Macitentan 10 mg (N = 40)	Previously on DB Placebo (N = 36)	All subjects (N=76)
6MWD	Yes*	Yes*	Yes*	Yes*
Borg dyspnea index	Yes*	Yes*	Yes*	Yes*
WHO FC	Yes*	Yes*	Yes*	Yes*

6MWD = 6 minute walk distance; DB = double-blind; NA = not applicable; OL = open-label; WHO FC = WHO functional class.
* Baseline as defined in MERIT-1 will be used for Macitentan 10 mg Merit (DB/OL) cohort. For the MERIT-2 summaries ('Previously on DB Placebo', 'Previously on DB Macitentan 10 mg' and 'All subjects'), baseline value is the last non-missing assessment obtained prior to the start of study drug intake in MERIT-2 OL.

8.5.1.1. Six-minute Walk Distance

Absolute change in meters from baseline to time point in the 6MWD defined as:

(6MWD(m) at time point − 6MWD(m) at baseline)

is the variable for the analysis of the exploratory endpoint, change from baseline to each scheduled time point in exercise capacity, as measured by the 6MWT.

8.5.1.2. Borg Dyspnea Index

Absolute change from baseline to time point in Borg dyspnea index defined as:

(*Borg dyspnea index at time point - Borg dyspnea index at baseline*)

is the variable for the analysis of the exploratory endpoint, change from baseline to each scheduled time point in Borg dyspnea index collected at the end of the 6MWT.

For Borg dyspnea index, the baseline value is the value reported at the same assessment as baseline 6MWD.

8.5.1.3. WHO Functional Class

Occurrence of worsening in WHO FC level at time point as compared to baseline (see definition in 8.3) is considered and the following dichotomous variable is defined:

$$X_i = \begin{cases} 1 \; if \; (Difference \; between \; time \; point \; and \; baseline \; in \; WHO \; FC) > 0 \\ 0 \; if \; (Difference \; between \; time \; point \; and \; baseline \; in \; WHO \; FC) \leq 0 \end{cases}$$

The proportion of subjects experiencing any increase in WHO FC level at time point as compared to baseline, defined as the proportion of subjects who have occurrence of worsening (Xi = 1) is the variable for the analysis of the exploratory endpoint, proportion of subjects with worsening of WHO FC from baseline to each scheduled time point.

8.5.2. Analysis of the Exploratory Efficacy Variables

Analysis of the exploratory efficacy endpoint variables will be conducted on the OLAS (Macitentan 10 mg MERIT-2 (OL) cohort) and RAS (Macitentan 10 mg MERIT (DB/OL) cohort), see Section 3.4 and Table 8:

- On the OLAS, as change from baseline of the OL extension study, by randomized treatment group in the DB core study.
- On the RAS, as change from baseline of the DB core study (single arm).

No imputation of data will be performed in the analysis of the exploratory endpoints.

In order to maximize the use of collected data and to analyze the data at relevant time points, a time-windowing approach (see Section 8.4) will be employed to include data from all study assessments up to EOS.

There is an assumption that the measurement of 6MWD and WHO were taken on the same dates based on visits planned in the Protocol. MERIT-2 OL dates of visits of the WHO endpoint are missing (sdtm: XP.XPDTC) but with reported values (sdtm: XP.XPSTRESC). In accordance with the Visit Windows rules (Section 8.4) these dates should be re-assigned to the most appropriate time point. In absence of these time points for WHO, the 6MWD dates (sdtm: XP.XPDTC) of coincident visits (sdtm: XP.VISIT) will be used for re-assignment.

8.5.2.1. 6-minute Walk Distance (m)

The summary tables based on observed values will be presented for 6MWD at baseline (MERIT-2, see Section 8.3), Month 6 (MERIT-2), Month 12 (MERIT-2), Month 18 (MERIT-2) and every 6 Months up to EOT visit on OLAS (Macitentan 10 mg MERIT-2 (OL) cohort) as defined in Table 8. The summary tables based on observed values will be presented for 6MWD at baseline (MERIT-1, see Section 8.3), Week 8 (MERIT-1), Week 16 (MERIT-1), Week 24 (MERIT-1; Baseline of MERIT-2), Month 6 (MERIT-2), Month 12 (MERIT-2), Month 18 (MERIT-2) and every 6 Months up to EOT visit on RAS (Macitentan 10 mg MERIT (DB/OL) cohort) as defined in Table 8.

The change in 6MWD from baseline to each timepoint defined above (both on the OLAS and RAS) will be displayed using descriptive statistics for continuous variables as described in Section 12.3 along with 95% two-sided confidence limits (CL) of means and medians.

In addition to summaries, the following graphical presentations of data will be provided for 6MWD:

- Box plots on change of 6MWD values from baseline over time (Month 6 (MERIT-2), Month 12 (MERIT-2), Month 18 (MERIT-2) and every 6 Months up to the EOT by DB randomized groups of the Macitentan 10 mg MERIT-2 (OL) cohort and at Week 8 (MERIT-1), Week 16 (MERIT-1), Week 24 (MERIT-1; Baseline of MERIT -2), Month 6 (MERIT-2), Month 12 (MERIT-2), Month 18 (MERIT-2) and every 6 Months up to EOT visit on Macitentan 10 mg MERIT (DB/OL) cohort), see Table 8.

8.5.2.1.1. Sensitivity analysis

To investigate the impact of 6MWT not performed according to Actelion guidelines, a sensitivity analysis will be performed. This analysis will be done as defined in section 8.5.2.1, excluding subjects for whom at least 1 protocol deviation "PD_MM.206: 6MWD at a 6-monthly visit not performed as per the Actelion Guidelines (except for deviations approved by Actelion)" reported in Merit-2 eCRF.

8.5.2.2. Borg Dyspnea Index

The summary tables based on observed OLAS and RAS values will be presented for the Borg dyspnea index at Baseline and each timepoint as described for 6MWD in Section 8.5.2.1.

In addition to summaries, the graphical presentations of data will be provided for Borg dyspnea index as it is described for 6MWD in Section 8.5.2.1.

8.5.2.3. WHO Functional Class

The proportion (with 95% CLs) of subjects worsening (subjects who have an occurrence of worsening (Xi = 1), see Section 8.5.1.3) by each post-baseline visit as defined for 6MWD in Section 8.5.2.1 will be summarized on Macitentan 10 mg MERIT-2 (OL) and Macitentan 10 mg MERIT (DB/OL) cohorts (see Table 8) and visualized by means of bar charts over time (see Section 8.5.2.1).

Observed WHO FC scores on the OLAS (Macitentan 10 mg MERIT-2 (OL) cohort, see Table 8) and on the RAS (Macitentan 10 mg MERIT (DB/OL) cohort, see Table 8) will be tabulated at baseline and each post-baseline visit as defined for 6MWD in Section 8.5.2.1. The separate summary table will be created for worsening in WHO FC at each post-baseline visit as defined for 6MWD in Section 8.5.2.1 in respect to baseline as defined in Section 8.5.1.3.

For the analyses based on the RAS (Macitentan 10 mg MERIT (DB/OL) cohort, see Table 8), a shift table will display the change in WHO FC from baseline (MERIT-1, see Section 8.3) to Week 8 (MERIT-1), Week 16 (MERIT-1), Week 24 (MERIT-1; Baseline of MERIT -2), Month 6 (MERIT-2), Month 12 (MERIT-2), Month 18 (MERIT-2) and every 6 Months up to EOT visit and based on the OLAS (Macitentan 10 mg MERIT-2 (OL) cohort, see Table 8), a shift table will display the change in WHO FC from baseline (MERIT-2, see Section 8.3) to Month 6, Month 12, Month 18 and every 6 Months up to EOT.

8.6. Safety

The following Safety and Tolerability variables will be considered in this study:

- Treatment-emergent AEs up to 30 days after study drug discontinuation.

- AEs leading to premature discontinuation of study drug.
- Treatment-emergent SAEs up to 30 days after study drug discontinuation.
- Treatment-emergent marked laboratory abnormalities up to 30 days after study drug discontinuation.
- Adverse events of special interest up to 30 days after study drug discontinuation
- Deaths.
- Change in vital signs (BP (DBP and SBP) and HR) and body weight from baseline to all assessed time points during the study.
- Laboratory parameters.
- Vital signs and body weight.
- Physical examination.

Table 9 – Safety Endpoints/Cohorts

	Macitentan 10 mg MERIT (DB/OL)	**MERIT-2 Macitentan 10 mg MERIT-2 OL**			**Macitentan 10 mg Pool**
	(N=40)	Previously on DB Macitentan 10 mg (N=40)	Previously on DB Placebo (N=36)	All subjects (N=76)	(N=76)
Exposure	Yes	Yes	Yes	Yes	Yes
AEs/SAEs/AESIs/AEs leading to permanent discontinuation*	Yes	Yes	Yes	Yes	Yes
Deaths	Yes	Yes	Yes	Yes	Yes
Vital Signs and body weight	Yes	Yes	Yes	Yes	Yes
Physical examination	Yes	Yes	Yes	Yes	Yes
Laboratory parameters	Yes	Yes	Yes	Yes	Yes

AE = adverse events; DB = double-blind, OL = open-label, SAEs = serious adverse events.
*AEs causing treatment premature discontinuations and AEs of special interest (hepatic events of special interest, edema and fluid retention, anemia and decrease of hemoglobin, hypotension) will also be summarized
Selected laboratory parameters will be also analyzed [Section 8.6.1.4].
For baseline definitions, see Section 8.3.

Note: *all safety endpoints will be evaluated up to EOS for subjects who enter a continued access program (UMBRELLA or PTA, see 'Study Drug Log' eCRF page) on the same day as the EOS visit, which corresponds to EOT visit in this case.*

8.6.1. Definition of Safety and Tolerability Variables

8.6.1.1. Treatment-emergent AE

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation until 30 days after EOT) with an onset date on the same date or after the date of first dose, or with a previous onset date but worsening severity (see definition in Section 8.6.1.1.1). Safety and tolerability endpoints will be analyzed for the combination of DB and OL periods:

- for the Macitentan 10 mg Pool cohort (see Section 3.4 and Table 9), with onset date ≥ start date (TRTSDT1 or TRTSDT2) and up to 30 days (inclusive) after EOT, or with an onset date before these dates but worsening severity after TRTSDT1 or TRTSDT2.
- for the Macitentan 10 mg MERIT (DB/OL) (see Section 3.4 and Table 9), with onset date ≥ start date (TRTSDT1) and up to 30 days (inclusive) after EOT, or with an onset date before these dates but worsening severity after TRTSDT1.

as well as for the OL period only:

- for the Macitentan 10 mg MERIT-2 (OL) (see Section 3.4 and Table 9), with onset date ≥ start date (TRTSDT2) and up to 30 days (inclusive) after EOT, or with an onset date before these dates but worsening severity after TRTSDT2.

AEs are reported by the investigator in the “Adverse Event” CRF form (see definition details in the Section 10.1.1 of the Protocol).

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.

Imputation of AE onset/resolution date is described in the Section 9.

AEs reported more than once (as qualified by the same PT) for a subject are counted only once in the frequency table.

8.6.1.1.1. Intensity of Adverse Events

The intensity of clinical AEs is graded on a three-point scale:

- Mild
- Moderate
- Severe

and is reported on “Adverse Event” eCRF form.

If the intensity of an AE worsens during study drug administration, only the worst intensity should have been reported on the AE page. If the AE lessens in intensity, no change in the severity was required.

8.6.1.1.2. Relationship to Study Drug

Relationship to study treatment is defined as ‘related’ or ‘not related’. An AE is considered related if the answer to the 'Is there a reasonable possibility that the Adverse Event was related to the use of study drug?' is checked as 'Yes' on the 'Adverse Event' CRF form. For treatment emergent AEs reported more than once (as qualified by the same PT) for a subject, the worst relationship (i.e., 'related') is considered. Adverse events with missing relationship are considered in any analysis as 'related'.

8.6.1.2. Adverse Events Leading to Premature Discontinuation of Study Drug

An AE is considered as leading to discontinuation of study treatment if the tick box ‘Permanently discontinued’ of ‘Action taken with study drug’ is checked in the Adverse Event CRF form.

8.6.1.3. Treatment-emergent Serious Adverse Events

An AE is considered serious if the tick box 'Yes' for 'Serious?' is checked on the 'Adverse Event' CRF form (see the details in Section 10.2.1 of the Protocol). If the information on seriousness is missing, the AE is assumed to be a SAE for the purpose of the summaries.

Treatment-emergent SAEs are determined as for TEAEs in Section 8.6.1.1.

8.6.1.4. Laboratory Parameters

A central laboratory data will be used for the analysis of all laboratory tests. The local laboratory data will be also used in the analyses of laboratory abnormalities.

Hematology and blood laboratory chemistry tests include all the parameters listed in Appendix 8.

8.6.1.4.1. Central Laboratory Alert Flags

On top of the flags described below, at a minimum, results above the upper limit or below the lower limit of the reference range for normal subjects will be flagged.

- Exclusionary Alert Value – At Enrollment (V1): The result is outside the study-specific defined limit for inclusion in the study.
  - Hemoglobin < 100 g/L
  - AST ≥ 3 × ULN
  - ALT ≥ 3 × ULN
- Total Bilirubin flag Alert Value – All visits except Enrollment (V1): In combination with ALT and/or AST ≥ 3 x ULN, study medication should be stopped.
  - Total bilirubin ≥ 2 x ULN
- Interruption or permanent discontinuation of study medication – All visits except Enrollment (V1):
  - AST ≥ 8 × ULN
  - ALT ≥ 8 × ULN
  - Hemoglobin < 80 g/L
  - Hemoglobin > 50 g/L decrease from baseline in MERIT-1 or in MERIT-2
- Repeat Alert value – All visits except Enrollment (V1):
  - AST ≥ 3 × ULN
  - ALT ≥ 3 × ULN
  - Hemoglobin > 20 g/L decrease from baseline in MERIT-1 or in MERIT-2

8.6.1.5. Treatment-emergent Marked Laboratory Abnormalities

TE MLAs are all marked laboratory abnormalities which occur during the DB/OL (OLSS and RAS Set, Table 6) or OL treatment-emergent period (OLAS Set, Table 6), that were not present at baseline (see Section 8.3).

Laboratory abnormalities according to the most updated version of common terminology criteria for adverse events (CTCAE).

A marked abnormality is defined based on the list (SI units) presented in Table 10.

Table 10 – Definition of Marked Laboratory Abnormalities

Parameter	LL	LLL	HH	HHH	HHHH
Hematology					
Hemoglobin (g/L)	< 100	< 80	Increase in (> 20 g/L above ULN) or above baseline if baseline is above ULN	Increase in (> 40 g/L above ULN) or above baseline if baseline is above ULN	NA
Hematocrit	< 28% for females < 32% for males	< 20%	> 60% in men > 55% in women	> 65%	NA
Platelet count (10^9 /L)	< 75	< 25	> 600	> 999	NA
Leucocytes (× 10e9 /L)	< 3.0	<2.0	> 20.0	> 100.0	NA
Neutrophils (10^9 /L)	< 1.5	<1.0	NA	NA	NA
Eosinophils			> 5.0 × 10e9 or > 5%	NA	NA
Lymphocyte (10^9 /L)	< 0.8	< 0.5	> 4.0	> 20.0	NA
Chemistry					
AST (U/L)	NA	NA	≥ 3 ULN	≥ 5 ULN	≥ 8 ULN
ALT (U/L)	NA	NA	≥ 3 ULN	≥ 5 ULN	≥ 8 ULN
AP	NA	NA	> 2.5 ULN	> 5 ULN	NA
Total bilirubin (umol/L)	NA	NA	≥ 2 ULN	≥ 5 ULN	NA
Parameter	**LL**	**LLL**	**HH**	**HHH**	**HHHH**
INR			> 1.5 × ULN or >1.5 times above baseline if on anticoagulation*	> 2.5 × ULN or > 2.5 times above baseline if on anticoagulation*	NA
Creatinine (umol/L)	NA	NA	> 1.5 ULN or 1.5 × baseline	> 3 ULN or > 3× baseline	NA

Glucose (mmol / L)	< 3.0	< 2.2	> 8.9	> 13.9	NA
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1	NA
Sodium (mmol/L)		< 130	> 150	> 155	NA
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0	NA
Magnesium (mmol/L)	< 0.5	< 0.4	NA	> 1.23	NA
Uric acid (mmol/L)	NA	NA	> 0.59	> 0.72	NA
Albumin (g/L)	< 30	< 20	NA	NA	NA
BUN	NA	NA	> 2.5 ULN	> 5 ULN	NA

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CTCAE = common terminology criteria for adverse events; LL / HH = marked abnormalities; LLL / HHH / HHHH = alert values; NA = not applicable; SI = international system of unit; ULN = upper limit of the normal range; INR = international normalized ratio. *For INR, a subject is considered to be on anticoagulation if the subject took antithrombotic agent (ATC codes B01A) and date of INR assessments is on or after start of anticoagulation therapy.

Note: changes implemented to this table are specified in Sections 8.6.1.4.1 and 8.6.2.6.1 and listed in Appendix 2

8.6.1.6. Vital Signs and Body Weight

Vital signs (systolic and diastolic blood pressures (SBP and DBP), pulse rate) and body weight are measured at Enrollment, Month 1, Month 6, and every 6 Months thereafter up to EOT + 30 days and reported in the "Vital Signs" CRF form.

Absolute change from baseline (Section 8.3) to each visit in SBP, DBP, pulse rate and body weight defined as (Value at visit X assessment available) - (value at baseline) will be calculated.

8.6.1.7. Physical Examination

Physical examination is performed at Enrollment (Visit 1), Month 1 (Visit 2), each 6-monthly visit (Visits 3, 4, 5…), EOT visit, and Safety follow-up / EOS visit.

Physical examination is recorded by body system in the eCRF as normal or abnormal. If an abnormality is detected, it must be specified in the eCRF, describing the signs related to the abnormality (e.g., systolic murmur) not the diagnosis (e.g., mitral valve insufficiency).

Data are retrieved from the SDTM PE domain.

8.6.1.8. Deaths

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

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

Treatment-emergent deaths are determined in the same way as for TEAEs according to the date of death.

8.6.2. Analysis of the Safety Variables

The OLSS, OLAS and RAS will be used to perform safety analyses. The RAS and OLSS analysis sets will be used for selected safety analyses as specified in Section 5.1.

All safety data will be included in listings, with flags for quantitative abnormalities.

Safety and tolerability endpoints will be analyzed for the combination of DB and OL periods (see Section 1.2.1).

8.6.2.1. Treatment-emergent Adverse Events

A table presenting an overall summary of the proportion of subjects with at least one AE as defined in Section 8.6.1.1, SAEs, AEs leading to treatment discontinuation and AESI (hepatic events of special interest (liver abnormalities), edema and fluid retention, anemia and decrease of hemoglobin, hypotension, see Appendix 7) and the proportion of deaths will be provided. Events occurring during the reporting DB and OL periods will be considered.

- The number and percentage of subjects experiencing treatment-emergent AEs at least once from baseline (see Section 8.3) up to 30 days following study drug discontinuation will be tabulated as defined in Table 9 and by:
- System organ class (SOC) and individual preferred term within each SOC, in descending order of incidence within the Macitentan 10 mg Pool cohort (see Table 9).
- Proportion of subjects with events coded with the same preferred term, in descending order of incidence within the Macitentan 10 mg Pool cohort (see Table 9).

Furthermore, all treatment-emergent AEs listed above occurring up to 30 days after study drug discontinuation will be tabulated as described above by severity and relationship to study drug.

A listing of all AEs with date of onset (as defined in Section 8.6.1.1) and up to 30 days (inclusive) after EOT will be provided with flags for quantitative abnormalities and SAEs.

To account for differences in exposure, incidence rates adjusted for subject-years for all AEs will be calculated in a similar manner as described for AESIs (Appendix 7).

8.6.2.2. Adverse Events Leading to Premature Discontinuation of Study Drug

The number and percentage of subjects experiencing at least one AE leading to discontinuation of study treatment up to EOT (see Section 8.3) will be tabulated and listed as described in Section 8.6.2.1.

8.6.2.3. Treatment-emergent Serious Adverse Events

The number and percentage of subjects experiencing at least one SAE will be presented by descending SOC/PT and descending PT frequency as described in Section 8.6.2.1.

A listing of all SAEs with date of onset over treatment period (see Section 3.3.1) and up to 30 days (inclusive) after EOT will be provided with flags for quantitative abnormalities.

8.6.2.4. Treatment-emergent Adverse Events of Special Interest

Treatment-emergent AESI (see Appendix 7) occurring up to 30 days after study drug discontinuation will be summarized as described in Section 8.6.2.1 (by SOC and PT).

In addition, serious treatment-emergent AESI occurring up to EOT + 30 days and treatment-emergent AESI leading to premature study drug discontinuation occurring up to EOT will be summarized as described above.

Listings for all AESI with date of onset (as defined in Section 8.6.1.1) and up to EOT + 30 days (inclusive) will be provided with flags for serious AESI. This listing will be supported by separate listing of treatment-emergent AESI up to EOT (inclusive) leading to premature drug discontinuation.

8.6.2.5. Laboratory Parameters

Descriptive summary statistics by visit and study treatment will be provided for observed values and absolute changes, from baseline up to EOT plus 30 days, in both hematology and blood chemistry laboratory tests. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 30 days will be assigned to the most appropriate visit time point (see Table 7) according to the best fitting time-window for that assessment.

The listings of all hematology and separately of blood chemistry parameters will be provided with corresponding flags as described in Section 8.6.1.4.1.

8.6.2.6. Treatment-emergent Marked Laboratory (Liver Test and Hemoglobin, Only) Abnormalities

Marked laboratory abnormalities will be summarized for each laboratory parameter providing their frequency and incidence (n (%) with the two-sided 95% CLs) for subjects with abnormalities.

Baseline laboratory values are defined as the latest values recorded before or on the date of the first dose of study medication (TRTSDT1 / TRTSDT2 (see baseline definition in the 8.3) for cohorts defined in Table 9). Baseline values are identified among test results from central laboratory. Post baseline values occurring within EOT + 30 days will be considered in the tables.

8.6.2.6.1. Liver Test Abnormalities (Including Unscheduled Visits)

Liver tests (LTs) for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin will be presented by incidence (n%) with two-sided 95% CLs using a binomial proportion, tabulated for subjects with abnormalities during the reporting period.

Hepatic abnormality criteria are specified below:

- (ALT ≥3 × upper limit of normal range [ULN]) OR (AST ≥3 × ULN)
- (ALT ≥5 × ULN) AND/OR (AST ≥ 5 × ULN)
- (ALT ≥8 × ULN) OR (AST ≥8 × ULN)
- Total Bilirubin ≥2 × ULN
- {(ALT ≥3 × ULN) AND/OR (AST≥3 × ULN)} AND (Total Bilirubin ≥2 × ULN)

- ALT AND/OR AST ≥3 AND <5 × ULN
- ALT AND/OR AST ≥5 AND <8 × ULN

For each subject, the worst abnormal value (i.e., the highest ALT, AST or total bilirubin values) will be considered and assigned to the appropriate category (may be more than one per subject).

- Using "evaluation of drug-induced serious hepatotoxicity" (eDISH) plots, graphical representations of total bilirubin versus ALT and of total bilirubin versus AST will be produced for cohorts defined in Table 9, to identify possible Hy's Law cases. The graph will present, for each subject, the peak total bilirubin × ULN against the peak ALT and AST × ULN in the same reporting period, on a log10 scale. Two reference lines will be plotted identifying the 2 × ULN for total bilirubin and 3 × ULN for ALT and AST. The peak is the maximum value from treatment start to last available assessment within the treatment period and up to EOT plus 30 days.

A listing will present all liver test data collected up to 30 days (inclusive) after EOT.

A supportive listing will be provided for subjects with liver abnormalities collected up to 30 days (inclusive) after EOT.

8.6.2.6.2. Incidence of Abnormal Hemoglobin Tests

- Subject counts (up to EOT + 30), percent (and corresponding two-sided 95% CLs), for the following categories of hemoglobin abnormality will be presented for cohorts defined in Table 9:
- Hemoglobin < 80 g/L
- Hemoglobin < 100 g/L
- 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.

For each subject, the worst abnormal value (i.e., the lowest hemoglobin value) will be considered and assigned to the appropriate category.

A listing will be provided and will present all hemoglobin collected up to 30 days (inclusive) after EOT. Clinically significant flags will be presented in accordance with the following changes from baseline:

- A decrease in hemoglobin to < 80 g/L (< 4.9 mmol/L)
- A decrease in hemoglobin from baseline of > 50 g/L

A supportive listing will be provided for subjects with hemoglobin abnormalities collected up to 30 days (inclusive) after EOT. Clinically significant flags will be presented as described above.

8.6.2.6.3. Liver Tests and Hemoglobin Abnormalities Adjusted for Subject-Years Exposure

To account for differences in exposure, incidence rates adjusted for subject-years for LTs and hemoglobin abnormalities will be calculated in a similar manner as described for AESIs (Appendix 7).

8.6.2.7. Vital Signs and Body Weight

Similarly to laboratory parameters, descriptive summary statistics by visit will be provided for observed values and absolute changes, from baseline up to EOT plus 30 days, both for vital signs and body weight. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT plus 30 days will be assigned to the most appropriate visit time point (see Table 7) according to the best fitting time window for that assessment.

A supportive listing will be provided for vital signs and body weight.

8.6.2.8. Physical Examination

Physical examinations performed during the study (see definition in Section 8.6.1.7) are reported in a subject listing.

8.6.2.9. Deaths

The number (and percentage) of subjects who died will be presented by SOC (with subjects counted once within each SOC), and cause of death (PT, with subjects counted once for each PT). SOC and PT will be presented by descending frequency based on the Macitentan 10 mg Pool cohort (see Table 9) and will include deaths occurring during the reporting period as defined in Section 8.6.1.1.

The tables above will also be repeated including all deaths that occurred from treatment start up to and beyond EOT + 30, i.e., all deaths reported in the database will be summarized by SOC and PT.

A listing of all deaths will be provided.

8.6.2.9.1. Estimation of Overall Survival

- Time to death (TTD; in months) will be estimated by the Kaplan-Meier (KM) product-limit method and summarized on RAS (Macitentan 10 mg DB/OL cohort) and OLSS (Macitentan 10 mg Pool cohort). The same approach as described for time to first occurrence of AESI (see Appendix 7) will be followed.

TTD (in days) and censoring flag (CENS) will be derived using the dates defined in Section 6 as:

Macitentan 10 mg DB/OL cohort

- TTD=DTHDT - TRTSDT1 and CENS=0 for subjects who died prior to EOT+30 days

  and

- TTD=min (LCTDT202, EOT+30 days) - TRTSDT1 and CENS=1 for subjects who did not die prior to EOT+30 days

Macitentan 10 mg Pool cohort

- TTD=DTHDT - TRTSDT1/TRTSDT2 (the start of the 10 mg therapy) and CENS=0 for subjects who died prior to EOT+30 days

  and

- TTD=min (LCTDT202, EOT+30 days) - TRTSDT1/TRTSDT2 (the start of the 10 mg therapy) and CENS=1 for subjects who did not die prior to EOT+30 days

TTD (in months) = TTD (in days) / 30.4375.

8.6.2.9.2. Follow-up

The median study follow-up will be estimated using the reverse Kaplan-Meier of long-term survival (Schemper 1996). It will be calculated in the same way as the KM estimate of the long-term survival (Section 8.6.2.9.1) but reversing censored subjects and deaths. Thus, in this analysis, death (CENS = 0) censors the true but unknown observation time of a subject and censoring in the survival analysis (CENS = 1) is an endpoint. The unobservable follow-up time of a deceased subject is interpreted as the follow-up time that potentially would have been obtained had that subject not died.

Median study follow-up will be presented with corresponding 25% and 75% percentiles and 95% confidence intervals using the method of Brookmeyer (Brookmeyer 1982).

9. HANDLING OF MISSING, INCOMPLETE OR INCONSISTENT DATE AND TIME VALUES

9.1. Handling Incomplete/Missing Dates

3. Dates are split into 3 parts: year, month and day. Year is the top level, month is medium level, and day is low level. If a part expected to contain a number is numeric but the value is outside a valid range, the complete date is handled as missing. For example, if date = 44Nov2000, the whole date is considered to be missing.
4. If a part expected to contain a number is not numeric, i.e., contains values such as for example ND, NA, --, ??, 2?, it is considered as missing.
5. If a part is missing, all other parts of a lower level are considered to be missing. This means that a ddmmyy date ‘21ND99’ is considered as ‘----99’.
6. Missing parts are changed into acceptable non-missing values in a way depending on the type of date to be replaced.

In Table 11, ‘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. All other missing or incomplete data not mentioned below are treated as missing.

Table 11 – Handling of Missing, Incomplete, or Inconsistent Date and Time Values

Type of date	Date is incomplete	Date is missing
Date of birth	Day missing: 15th of the month Day and month missing: 30th of June	No replacement
Date of death (DTHDT)	Use the lower limit	No replacement
AE resolution date	The upper limit	No approximation, the AE is considered as ongoing.
AE onset date	If the end date of the AE is not before the start of study treatment, and if the study treatment start falls in the range of possible dates, it is the study treatment start date. In all other cases, it is the lower limit. Of note, treatment start date is TRTSDT1 for macitentan 10 mg MERIT (DB/OL), TRTSDT2 for macitentan 10 mg MERIT-2 (OL), TRTSDT1 or TRTSDT2 for Macitentan 10 mg pool.	The earlier of the date of resolution of the AE and the study treatment start date (TRTSDT1 for macitentan 10 mg MERIT [DB/OL], TRTSDT2 for macitentan 10 mg MERIT-2 [OL] and TRTSDT1/TRTSDT2 for macitentan 10 mg pool).
Concomitant medication start date	Lower limit except when: Not tagged as ongoing at start of treatment in Macitentan 10 mg OL AND Medication stop date not collected or with the upper limit after study drug start AND the treatment start day falls in the range of possible dates. In which case it is the study drug start day	No replacement, the therapy is considered to have started before the study
Concomitant therapy end date	Upper limit except when: Therapy start is before study treatment start or missing AND Upper limit is after the study treatment start AND Not tagged as ongoing at start of treatment In which case it is 1 day before study treatment start.	No replacement (considered ongoing)
End-of-Treatment°	Use the earliest date between the: • upper limit • last contact date* • date of death	Use the earliest date between the: • last contact date* • date of death For Chinese subjects only: • CUTOFDT

Type of date	Date is incomplete	Date is missing
End-of-Study°	Use the earliest date between the: • upper limit • last contact date* • date of death	Use the earliest date between the: • last contact date* • date of death For Chinese subjects only: • CUTOFDT
Death date	Use the lower limit	No replacement

* Last contact date is the date of the last visit, or, in case of loss to follow-up, the date of the last successful contact attempt (as reported in SDTM DS domain under DSTERM = "LAST CONTACT"

° please note that for subjects who enter a continued access program (UMBRELLA or PTA, see 'Study Drug Log' eCRF page) on the same day as the EOS visit, EOS corresponds to EOT visit in this case.

10. OTHER SAFETY ANALYSES

10.1. Extent of Exposure

Analysis of exposure to study drug will be conducted on the OLAS, RAS and OLSS analysis sets (see Section 3.4 and Table 6).

Treatment duration of study drug will be described in terms of duration in months and years and produced for each cohort (see Section 5.1). The duration of treatment is defined as the timeelapsing between study drug initiation and discontinuation, inclusive, regardless of treatment interruptions. The treatment duration (expressed in months and years) will be tabulated using the usual location and scale summary statistics for continuous variable (see Section 8.1).

The cumulative treatment duration will be displayed per 6-month interval over time. Subject-year exposure will also be displayed and will be derived as the duration of exposure for which each subject received treatment, as defined above, divided by 365.25. The total subject-years of a treatment group is the sum over individual subjects in each cohort defined below.

Treatment duration is the number of days a subject was on treatment, regardless of interruptions.

- For subjects in the 'Macitentan 10 mg MERIT (DB/OL)' cohort:

  Duration (days) = TRTEDT2 – TRTSDT1 +1

- For subjects in the 'Macitentan 10 mg MERIT-2 (OL)' cohort:

  Duration (days) = TRTEDT2 – TRTSDT2 +1

- For subjects in the 'Macitentan 10 mg Pool' cohort:

  Duration (days) = TRTEDT2 – TRTSDT1 +1 - if subject starts macitentan treatment in MERIT-1.

  Duration (days) = TRTEDT2 – TRTSDT2 +1 - if subject starts macitentan treatment in MERIT-2.

  Duration (months) = Duration (days)/30.4375

Duration (years) = Duration (days)/ 365.25

10.2. Treatment Compliance

The mean daily dose per subject is defined as the ratio between the total study drug dose (number of tablets provided to subject − number of tablets returned) taken during the treatment period and the total exposure time.

Compliance, in percent, is defined as percent of doses taken divided by expected number of doses during follow-up:

Compliance = [(number of tablets provided to subject − number of tablets returned) /

Total number of tablets that should have been taken during the period] ×100

where the total number of tablets that should have been taken during the period is defined as:

$$(treatment\ end\ date - treatment\ start\ date + 1)$$

The compliance with study drug intake < 80% or > 120% will be also reported in summary tables per each cohort defined above

Mean daily dose and study treatment compliance will be tabulated using the usual location and scale summary statistics (see Section 8.1).

All information will be also presented in subject listings with corresponding flags for the compliance with study drug intake < 80% or > 120%. Reasons for not dispensing the assigned treatment to a participant will be also reported in listing at each accountability visit (Month 1, Month 2, Month 6 and every 6 months thereafter).

11. DATA MONITORING COMMITTEE (DMC) OR OTHER REVIEW BOARD

- The same Steering Committee (SC) as the one involved in the AC-055E201 / MERIT-1 study was involved in the MERIT-2 study design and will provide guidance on the conduct of the study.

An independent International Liver Safety Data Review Board (ILSDRB): an external expert committee of hepatologists provided ongoing assessment and advice regarding serious hepatic events that required further evaluation during the study.

12. SUPPORTING DOCUMENTATION

12.1. Appendix 1 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CL	Confidence limits
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTEPH	Chronic thromboembolic pulmonary hypertension
DB	Double-blind
DBP	Diastolic blood pressure
DTHDT	Date of death
eCRF	Electronic case report form
EOS	End-of-Study
EOT	End-of-Treatment
ERA	Endothelin receptor antagonist
FC	Functional class
FDA	Food and Drug Administration
INR	International normalized ratio
IXRS	Interactive voice/web recognition system
LCTDT202	MERIT-2 OL last contact date
LT	Liver test
LSAF	Life Science Analytics Framework
MedDRA	Medical Dictionary for Regulatory Activities
MERIT	Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
OL	Open-label
OLAS	Open-Label Analysis Set
OLSS	Open-Label Safety Set
PEA	Pulmonary endarterectomy
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RAS	Restricted Analysis Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Steering committee
SOC	System organ class
SOP	Standard operating procedure
TIBC	Total iron binding capacity
TRTEDT1	End date of treatment in MERIT-1 DB
TRTEDT2	End date of treatment in MERIT-2 OL
TRTSDT1	Start date of macitentan in MERIT-1 DB
TRTSDT2	Start date of macitentan in MERIT-2 OL
TTD	Time to death
ULN	Upper limit of the normal range
WHO	World Health Organization

12.2. Appendix 2 Changes to Protocol-Planned Analyses

1. The definition of adverse events of special interest (AESI) and their evaluations were embedded in this SAP (see Appendix 7) to be consistent with other macitentan studies.
2. The statistical analyses to evaluate the differences in efficacy of treatment in randomized treatment arms as specified in the Protocol (11.3.3.1 and 11.3.3.2) were excluded from current analyses (see Section 8.5.2) due to the single-arm study design.
3. The RAS analysis set will be used to assess the long-term survival on subjects who was on 10 mg study treatment from the start of treatment in the DB and up to EOS in the OL as well as in the assessment of AEs and Deaths.
4. The OLSS analysis set will be used to assess the long-term survival on subjects who had any time 10 mg macitentan from the start of treatment in the DB or OL and up to EOS in the DB or OL whichever comes later.
5. The duration of treatment exposure will be assessed on all analysis sets, OLAS, RAS and OLSS.
6. For consistency with the Macitentan/UNISUS study, in the hepatic abnormality criteria were included subjects who had values higher ***OR EQUAL*** to ULN for ALT, AST and bilirubin parameters.
7. The local laboratory data will be also used in the analyses of laboratory abnormalities.
8. Serum pregnancy test positive flags were excluded from alert flags (see Section 8.6.1.4.1 of the SAP and Appendix 5 of the Protocol) as were not reported in the eCRF.
9. The baseline in MERIT-2 was added to central laboratory alert flags for change from baseline in hemoglobin as far as flags are considered in listings and laboratory tests will be listed based on OLSS analysis set, where for subjects who started macitentan 10 mg in OL trial, the MERIT-2 baseline only is considered (see changes in Section 8.6.1.4.1).
10. Sensitivity analysis for 6MWD endpoint was implemented as defined in section 8.5.2.1 excluding those subjects for whom there is at least one protocol deviation “PD_MM.206: 6MWD at a 6-monthly visit not performed as per the Actelion Guidelines (except for deviations approved by Actelion)” reported in Merit-2 eCRF.
11. Additional rules were added in section 8.6.2.6.1 to align them with Macitentan/UNISUS study, i.e. ALT AND/OR AST ≥3 AND <5 × ULN and ALT AND/OR AST ≥5 AND <8 × ULN

12.3. Appendix 3 Demographics and Baseline Characteristics

Demographics, and baseline characteristics will be summarized by each cohort as appropriate (see Table 6 and Section 3.4).

- Continuous variables (e.g., 6MWD, Borg dyspnea score or cardiac output, etc.) will be summarized by the number of non-missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum will be presented.
- For dichotomous or categorical variables (e.g., age, sex, geographical region, etc.), the number of non-missing observations, and frequency with percentage per category will be presented. Denominators for percentages are the number of subjects in corresponding cohort (see Table 6 and Section 3.4), unless otherwise specified.

Baseline demographic, height, and disease characteristics of interest for this OL study will be taken from the AC-055E201 / MERIT-1 database.

12.3.1 Demographics

The MERIT-2 OL baseline demographics will be summarized using descriptive statistics for continuous or categorical variables as defined in Section 12.3.

The number of subjects in each analysis set will be summarized and listed. In addition, the distribution of subjects by region, country and site ID will be presented unless otherwise noted.

Summaries for demographic characteristics will be performed on the OLAS (see Table 6 and Section 3.4). The variables in Table 12 will be summarized per originally randomized treatment group and overall.

Table 12 – Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (< 18; ≥18 and <65; ≥65 and <85; ≥ 85 years)	Frequency distribution with the number and percentage of subjects in each category.
Age (< 65, ≥ 65 years)	
Sex (male, female)	
Race (White, Asian)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Childbearing potential status (Yes/No), and reason (why a female is considered not to be of childbearing potential)	
Geographical region (Asia, Eastern Europe, Western Europe, Latin America)	

Age (years) at the start of treatment in the OL is referred to date at screening in the DB (MERIT-1) and will be reported as number of completed years.

12.4. Appendix 4 Protocol Deviations

The description of each protocol deviation (PD) is agreed in the sponsor Protocol Deviation Code List (TPL-100062) specific for this study. According to this document, each PD is classified as major or not and categorized into periods as follows:

- Protocol Deviation before enrollment.
- Protocol Deviation at Study Entry (enrolled in IXRS).
- Protocol Deviation during treatment period and follow-up (see Table 6).

Protocol deviations will be summarized by category, displaying counts and percentages of subjects with at least one PD for the OLAS Set (Macitentan 10 mg OL cohort, see Section 3.4). A similar table is presented for major protocol deviations (related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment).

This summary table is sorted, within each category, by frequency, in descending order according to the incidence in the 'All subjects' column of the ‘Macitentan 10 mg MERIT-2 (OL)’ cohort (with the highest number of occurrences appear first); if a tie occurs, the tied characteristics will be sorted alphabetically. This will be supported by a summary table of major protocol deviations. Major protocol deviations will be displayed by region, country, and site.

All reported PDs will be reported in a subject listing broken down by region, country, and site. Major PDs will be flagged accordingly.

12.5. Appendix 5 Concomitant Medications

A concomitant medication is any medication that started, stopped, or was ongoing between Enrollment (first dose of OL study drug, TRTSDT2) and last subject's visit (LCTDT202):

Concomitant medication is defined as any medication that is taken at the start of study drug (TRTSDT2). This includes any medication with the tick box "ongoing" checked, or with a start date before or on the day of study drug start (TRTSDT2) and the end date not before study drug start (TRTSDT2). Start and end dates that are incomplete will be handled according to the rules for partial and missing concomitant medication dates in Section 9.

Concomitant medications will be reviewed at each visit.

Study-treatment concomitant therapies are summarized by Anatomical Therapeutic Chemical (ATC) class and PT Enrollment (Visit 1) up to 30 days after study drug discontinuation (EOS visit).

A listing of all study-treatment concomitant medications with onset date up to 30 days after EOT (after study drug discontinuation (EOS visit)) will be provided.

Methods of contraception are collected in the Contraceptive Methods Log page of the eCRF. Change in childbearing potential status is collected in the Childbearing Potential Status Change page of the eCRF. A supportive listing will be provided for childbearing potential and contraception on female population.

The summary tables are presented in descending order according to the incidence in the 'All subjects' column of the 'Macitentan 10 mg MERIT-2 (OL)' cohort (i.e., ATC and individual PT within each ATC with the highest number of occurrences appear first). Equal frequency of different ATC / individual PTs is sorted in alphabetical order of the ATC / individual PT.

Start and end dates that are incomplete are handled according to the rules for partial and missing concomitant medication dates; refer to Section 9.

12.5.1 Special Interest Category: PAH therapies

Concomitant medications of special interest, ie, PAH therapies, are defined as follows:

Endothelin Receptor Antagonists (ERAs):

Ambrisentan,

Bosentan,

Macitentan

Phosphodiesterase Inhibitors (PDE 5 Inhibitors):

Sildenafil,

Tadalafil,

Vardenafil

Prostacyclin Analogue:

Oral Treprostinil,

Beraprost

Inhalated prostacyclins:

Iloprost,

Inhaled Treprostinil

Selective IP Receptor Agonist:

Selexipag

Soluble Guanylate Cyclase (sGC) Stimulators:

Riociguat

Intravenous and subcutaneous Treprostinil

Epoprostenol

Note: subjects may receive more than one treatment and may be included in more than one treatment class.

Concomitant medications of special interest, ie, PAH therapies, will be summarized in the same way as concomitant medications, see Section 12.5. A participant listing of concomitant medications of special interest will also be provided.

12.6. Appendix 7 Adverse Events of Special Interest

The number and percentage of subjects experiencing at least one AESI will be presented similarly to other treatment-emergent adverse events, as described in Section 8.6.2.1, by descending SOC and PT frequencies based on the "Macitentan 10 mg Pool" cohort (see Table 9).

Separate listing will be provided for each AESI.

The following groups of AESIs are considered:

- **Hepatic events of special interest**

Any treatment-emergent AE (see definition in Section 8.6.1.1) included in the following grouping.

SMQ Drug related hepatic disorders – comprehensive search (includes all sub-SMQs within), excluding sub-SMQ:

Liver-related coagulation and bleeding disturbances,

and excluding PTs:

Ascites

Bacterascites

Biliary ascites

Haemorrhagic ascites

- **Edema and fluid retention**

Any treatment-emergent AE (see definition in Section 8.6.1.1) with PT listed in the Standardized MedDRA Query (SMQ) 'Haemodynamic oedema, effusions and fluid overload (SMQ)' or with PT equal to 'Pulmonary congestion' defined in the latest available MedDRA version with the exception of PTs containing 'site'.

- **Anemia**

Any treatment-emergent AE (see definition in Section 8.6.1.1) with a PT within the SMQs 'Haematopoietic erythropenia' 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**

Any treatment-emergent AE in accordance with the Standardized MedDRA query (SMQ):

1)Actelion AMQ hypotension:

- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure immeasurable
- Blood pressure orthostatic decreased

- Blood pressure systolic decreased
- Blood pressure systolic inspiratory decreased
- CT hypotension complex
- Diastolic hypotension
- Hypotension
- Mean arterial pressure decreased
- Neonatal hypotension
- Orthostatic hypotension
- Post procedural Hypotension
- Procedural hypotension

excluding PTs: Neonatal hypotension, Postoperative hypotension, Post procedural Hypotension, Procedural hypotension.

2) Actelion AMQ symptomatic hypotension (selected PTs only):

- Acute hypotension
- Blood pressure ambulatory decreased
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure immeasurable
- Blood pressure orthostatic decreased
- Blood pressure systolic decreased
- Blood pressure systolic inspiratory decreased
- Circulatory collapse
- CT hypotension complex
- Diastolic hypotension
- Dizziness
- Dizziness postural
- Fall
- Hypotension
- Hypotension paroxysm
- Hypotension symptomatic
- Loss of consciousness
- Mean arterial pressure decreased
- Neonatal hypotension

- Orthostatic hypotension
- Persistent postural-perceptual dizziness
- Postoperative hypotensionPost procedural Hypotension
- Preshock
- Presyncope
- Procedural hypotension
- Shock
- Shock symptom
- Syncope
- Vertigo

Note: Any modifications of terms may occur based on later dictionary updates and/or external guidance.

Only the following PTs within this AMQ are included:

- Acute hypotension
- Circulatory collapse
- Loss of consciousness
- Presyncope
- Shock
- Shock symptom
- Syncope

12.6.1 AESI adjusted for subject-years exposure

Incidence rates of treatment-emergent AESIs will be presented as adjusted for number of subject-years (SY) exposure.

The following method will be applied for adjusted incidence rates:

Person-time will be calculated by summing the days of treatment duration for each subject.

Subject-year exposure (SYE) will be calculated by dividing the total subject time by 365.25 days.

The incidence rate for an AE per 100 person-years will be calculated by dividing the number of subjects with AEs by the SYE and multiplying by 100.

Adjusted Incidence Rate = 100 × (Number of subjects with at least one treatment-emergent AE/SYE).

Subjects without event are censored at EOT+30.

The adjusted incidence rate is interpreted as the number of events occurring in 100 subject-years. It is based on the assumption that the occurrences of a specific event are following an independent

Poisson process, so the events occur with a constant rate over time. Hence, the 95% CLs of the adjusted incidence rate will be computed using a Poisson regression model with log of time at risk as an offset (SAS PROC GENMOD; see Appendix 9 for code example).

The following information will be displayed:

n = The number of subjects with at least one event. Subjects with multiple events will be counted only once (only the initial event will be counted).

T = The total of the subject's time on treatment in years.

Adj Rate = The adjusted event incidence rate per 100-SY. It is interpreted as the number of events occurring in 100-SY.

Note: these rates will only be presented overall and not at a PT level.

12.6.2 Time to first occurrence of AESI

Time to first occurrence of treatment-emergent AESI will be estimated by the Kaplan-Meier (KM) product-limit method and summarized for Macitentan 10 mg MERIT (DB/OL), Macitentan 10 mg MERIT Pool and Macitentan 10 mg MERIT (OL) cohorts at pre-specified time points (e.g., 6 months, 12 months, etc.), number of subjects at risk, number of subjects with event (%), number of subjects censored (%), KM estimates, and 95% CLs. The standard error of the KM estimate will be calculated using Greenwood's formula (Collett 1994).

Time to occurrence will be limited to time to first occurrence of event of interest. Subjects with no events will be censored as presented in Table 13.

KM plots for time to AESI will be truncated at the timepoint after which less than 10% of the subjects remain at risk (Pocock 2002).

The following table describes various situations for events and the rules for handling them. If more than one situation applies, the rule for the first applicable date is to be followed.

Censoring rules for time to first occurrence of AESI are presented in Table 13.

Table 13 – Censoring rules for time to first occurrence of the treatment-emergent AESI

	Situation	Time to Event		Status of time-to-event variable
		Start-date	**End-date**	
A	Subject with an event*	Date start of study treatment	Date of first onset of AE	Event
B	Subject died	Date start of study treatment	Date of death if occurring on or before 30 days after end of treatment.	Censor
C	Subject with no event (subject discontinued from the study treatment)	Date start of study treatment	EOT + 30 days	Censor
D	Subject with no event (subject still on treatment)	Date start of study treatment	EOT + 30 days	Censor

* Event is the first occurrence of AESI. AE = adverse event; AESI = AE of special interest; EOT = End-of-Treatment.

12.8. Appendix 8 Central Laboratory Normal Ranges

Test Name Full	Department	Age Low	Age Low Unit	Age High	Age High Unit	Sex	Conv. Ref. Interval Low	Conv. Ref. Interval High	Conv. Unit	Conv. Factor SI to Conv	SI Ref. Interval Low	SI Ref. Interval High	SI Unit	Conv. Report limit Low	SI Report limit Low
Hemoglobin	Hematology	15	y	999	y	M	13.5	17.5	g/dL	0.1	135	175	g/L		
Hemoglobin	Hematology	15	y	999	y	F	12.0	16.0	g/dL	0.1	120	160	g/L		
Hematocrit	Hematology	15	y	999	y	M	40	52	%	100	0.40	0.52	L/L		
Hematocrit	Hematology	15	y	999	y	F	36	46	%	100	0.36	0.46	L/L		
Erythrocyte Count	Hematology	15	y	999	y	M	4.6	5.8	x10E6/uL	1	4.6	5.8	x10E12/L		
Erythrocyte Count	Hematology	15	y	999	y	F	4.1	5.2	x10E6/uL	1	4.1	5.2	x10E12/L		
MCV	Hematology	15	y	999	y	M/F	81	98	fL	1	81	98	fL		
MCH	Hematology	5	y	999	y	M/F	27	34	pg	1	27	34	pg		
MCHC	Hematology	5	y	999	y	M/F	32.0	37.0	g/dL	0.1	320	370	g/L		
Leukocyte Count	Hematology	5	y	999	y	M/F	4.0	10.7	x10E3/uL	1	4.0	10.7	x10E9/L		
Neutrophils (%)	Hematology	7	y	999	y	M/F	43	74	%	1	43	74	%		
Total Lymphs (%)	Hematology	13	y	999	y	M/F	20	44	%	1	20	44	%		
Monocytes (%)	Hematology	7	y	999	y	M/F	3	10	%	1	3	10	%		
Eosinophils (%)	Hematology	13	y	999	y	M/F	0	7	%	1	0	7	%		
Basophils (%)	Hematology	31	d	999	y	M/F	0	2	%	1	0	2	%		
Neutrophils (Abs)	Hematology	7	y	999	y	M/F	1.6	7.4	x10E3/uL	1	1.6	7.4	x10E9/L		
Total Lymphs (Abs)	Hematology	13	y	999	y	M/F	1.0	4.0	x10E3/uL	1	1.0	4.0	x10E9/L		
Monocytes (Abs)	Hematology	7	y	999	y	M/F	0.1	0.9	x10E3/uL	1	0.1	0.9	x10E9/L		
Eosinophils (Abs)	Hematology	13	y	999	y	M/F	0.0	0.7	x10E3/uL	1	0.0	0.7	x10E9/L		
Basophils (Abs)	Hematology	31	d	999	y	M/F	0.0	0.2	x10E3/uL	1	0.0	0.2	x10E9/L		
Platelets count	Hematology	15	y	999	y	M/F	150	350	x10E3/uL	1	150	350	x10E9/L		
Reticulocytes (%)	Hematology	18	y	999	y	M/F	0.7	2.5	%	1	0.7	2.5	%		
Reticulocytes (Abs)	Hematology	18	y	999	y	M/F	30	110	x10E3/uL	1	30	110	x10E9/L		
Iron	Hematology	0	y	999	y	M	59	178	ug/dL	5.58	11	32	umol/L	5	1
Iron	Hematology	0	y	999	y	F	37	173	ug/dL	5.58	7	31	umol/L	5	1
Ferritin	Hematology	0	y	999	y	M	22	322	ug/L	1	22	322	ug/L		
Ferritin	Hematology	0	y	999	y	F	10	291	ug/L	1	10	291	ug/L		
Transferrin Saturation	Hematology	0	y	999	y	M/F	20	55	%	1	20	55	%		

Test Name Full	Department	Age Low	Age Low Unit	Age High	Age High Unit	Sex	Conv. Ref. Interval Low	Conv. Ref. Interval High	Conv. Unit	Conv. Factor SI to Conv	SI Ref. Interval Low	SI Ref. Interval High	SI Unit	Conv. Report limit Low	SI Report limit Low
TIBC	Hematology	0	y	999	y	M/F	250	452	ug/dL	5.58	45	81	umol/L		
Sodium	Chemistry	0	y	999	y	M/F	135	148	mmol/L	1	135	148	mmol/L		
Potassium	Chemistry	0	y	999	y	M/F	3.5	5.3	mmol/L	1	3.5	5.3	mmol/L		
BUN (Urea)	Chemistry	16	y	18	y	M/F	5	20	mg/dL	2.801	1.8	7.1	mmol/L	2.0	0.9
BUN (Urea)	Chemistry	19	y	999	y	M/F	6	25	mg/dL	2.801	2.1	8.9	mmol/L	2.0	0.9
Creatinine	Chemistry	13	y	18	y	M	0.35	1.20	mg/dL	0.0113	31	106	umol/L	0.20	18
Creatinine	Chemistry	13	y	18	y	F	0.46	1.00	mg/dL	0.0113	41	88	umol/L	0.20	18
Creatinine	Chemistry	19	y	999	y	M	0.70	1.20	mg/dL	0.0113	62	106	umol/L	0.20	18
Creatinine	Chemistry	19	y	999	y	F	0.50	0.91	mg/dL	0.0113	44	80	umol/L	0.20	18
Uric Acid	Chemistry	16	y	59	y	M	4.0	8.5	mg/dL	16.8	0.24	0.51	mmol/L	0.2	0.01
Uric Acid	Chemistry	16	y	999	y	F	2.5	7.5	mg/dL	16.8	0.15	0.45	mmol/L	0.2	0.01
Uric Acid	Chemistry	60	y	999	y	M	3.4	8.7	mg/dL	16.8	0.20	0.52	mmol/L	0.2	0.01
Albumin	Chemistry	0	y	999	y	M/F	3.2	5.5	g/dL	0.1	32	55	g/L		
Total Bilirubin	Chemistry	8	d	999	y	M/F	0.1	1.2	mg/dL	0.0585	2	21	umol/L	0.1	2
Direct Bilirubin	Chemistry	0	y	999	y	M/F	0.0	0.4	mg/dL	0.0585	0	7	umol/L	0	0
Indirect Bilirubin	Chemistry	0	y	999	y	M/F	0.0	0.7	mg/dL	0.0585	0	12	umol/L		
AST	Chemistry	7	y	999	y	M/F	0	41	U/L	1	0	41	U/L	4	4
ALT	Chemistry	10	y	18	y	M	5	30	U/L	1	5	30	U/L	4	4
ALT	Chemistry	10	y	18	y	F	5	20	U/L	1	5	20	U/L	4	4
ALT	Chemistry	19	y	999	y	M/F	0	45	U/L	1	0	45	U/L	4	4
AP (Alk Phos)	Chemistry	18	y	999	y	M	40	129	U/L	1	40	129	U/L	1	1
AP (Alk Phos)	Chemistry	18	y	999	y	F	35	104	U/L	1	35	104	U/L	1	1
LDH	Chemistry	16	y	999	y	M	100	242	U/L	1	100	242	U/L	5	5
LDH	Chemistry	16	y	999	y	F	100	220	U/L	1	100	220	U/L	5	5
Glucose	Chemistry	0	y	999	y	M/F	70	140	mg/dL	18.01477	3.9	7.8	mmol/L		
Calcium	Chemistry	0	y	999	y	M/F	8.6	10.5	mg/dL	4.0	2.14	2.62	mmol/L		
Magnesium	Chemistry	0	y	999	y	M/F	1.8	2.4	mg/dL	2.43	0.74	0.99	mmol/L	0.1	0.03
*Pregnancy (serum)	Immuno-chemistry	0	y	999	y	F	0	9	mIU/mL	1	0	9	IU/L	2	2

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean cell volume; SI = international system of unit; TIBC = total iron binding capacity; * Pregnancy (serum) is reported in the eCRF as Choriogonadotropin Beta

12.9. Appendix 9 Example SAS Code for Adjusted Incidence Rates and 95% CL

Note: time should be in years for GENMOD

```
** example code to show derivation of adjusted rate and CI based on
dummy data ** ;
** Create dummy data **;
 data aA;
  tot_eve=0;
  tot_time=0;
  do pn=1 to 110;
    time=ranuni(546546)*1000; ** time to event**;
    eve=(ranuni(5454)<.10);   ** event or censor **;
    tot_eve+eve;
    tot_time+time;
    l_time=log(time/365.25);
    if pn=110 then do;
      incidence=100*tot_eve/(tot_time/365.25); **incidence rate **;
    end;
    output;
  end;
run;

proc genmod data=aa;
  model eve= / dist=poisson link=log offset=l_time; /*** here is the
exposure time in offset***/
  output out=out p=pcount xbeta=xb stdxbeta=std;
  ods output ParameterEstimates=param;
run;

data predrates;
  set out;
  obsrate=eve/time;          /* observed rate */
  lograte=xb-l time;
  prate=100*exp(lograte);    /* predicted rate */
  lcl=100*exp(lograte-probit(.975)*std); ** Lower Limit **;
  ucl=100*exp(lograte+probit(.975)*std); ** upper Limit **;
run;

** derivation also available in PARAM**;
data param2;
  set param(WHERE=(parameter=("Intercept")));
  prate=100*exp(estimate);
  lcl=100*exp(LowerWaldCL);
  ucl=100*exp(UpperWaldCL);
run;
```

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Actelion Pharmaceuticals Ltd.

Statistical Analysis Plan for COVID-19 Impact Assessment

Long term, multicenter, single-arm, open-label extension study of the MERIT-1study, to assess the safety, tolerability and efficacy of macitentan in subjects within operable chronic thromboembolic pulmonary hypertension (CTEPH)
MERIT-2: Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension (Open-Label)

Protocol AC-055E202; Phase 2

JNJ - 67896062 / ACT-064992 (Macitentan)

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Date:	19 November 2021
Prepared by:	Actelion Pharmaceuticals Ltd., a Janssen Pharmaceutical Company of Johnson & Johnson
Document No.:	EDMS-589874, 1.0

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	19 November 2021	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses to assess the impact of the COVID-19 pandemic in the open-label study AC-055E202 (MERIT-2), following the guidance within the COVID-19 Standard Reporting Guideline Principles. This document is a separate Appendix of the Clinical Study Report (CSR) SAP of this study.

This SAP refers to the documents listed in Table 2.

Table 2 – Study Documents

Document	Date, Version
Study Protocol AC-055E202 (MERIT-2)	V4, 22 Jun 2021
Study Protocol AC-055E202 COVID-19 Appendix	Final Version, 21 Jun 2021 (D-20.282)
SAP for CSR AC-055E202 (MERIT-2)	Draft Version, 03 September 2021

Source data for the analyses will be Analysis Data Model (ADaM) data sets derived for the AC-055E202 (MERIT-2) CSR.

Except where otherwise specified, all definitions and conventions used in the CSR SAP of this study will be applied.

1.1. Objectives

To assess the impact of COVID-19 pandemic on:

1. Protocol deviations.
2. Extent of exposure to study drug.
3. Subject disposition information.
4. Safety (including AEs, deaths, vital signs, and laboratory assessments).
5. Concomitant medications.

1.2. Study Design

The study design is described in Section 3.1 of the study protocol.

2. STATISTICAL HYPOTHESES

Not applicable for the scope of this document.

3. SAMPLE SIZE DETERMINATION

Not applicable for the scope of this document.

The sample size in the OL study was based on the number of subjects in the DB study that were eligible to transition to the OL study (see section 2.1 of the CSR SAP for details).

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The OLAS, RAS and OLSS analysis sets described in section 3.0 of the CSR SAP will be used in current analyses as appropriate.

5. STATISTICAL ANALYSES

5.1. General Definitions

5.1.1. COVID-19 Periods of the Pandemic

Based on the declaration by the World Health Organization Director-General at the media briefing on COVID-19 on March 11th, 2020, COVID-19 can be characterized as a pandemic and its periods could be identified as follows:

Table 3 – COVID-19 periods of the pandemic

Period	Definition
Pre COVID-19	Defined as the period before March 11th, 2020 unless there is prior evidence of COVID-19 by the data collection. In that case, March, 11th 2020 is replaced by the date of the first evidence of COVID-19 (see definition below).
During COVID-19*	Defined as the period between March 11th 2020 (or earlier in case of prior evidence of COVID-19) and the end date of the pandemic (limits included) or the date of the study closure, whichever comes first.
Post COVID-19*	Defined as the period starting immediately after the end date of pandemic onwards.

* Given that the pandemic still ongoing at the time of this document, no end date of the pandemic is available. Therefore, an open end is set for the 'During COVID-19' period and the 'Post COVID-19' period cannot be considered for the analyses.

Prior evidence of COVID-19 (i.e., before March, 11th 2020) can be identified as follows:

- **Date of premature study treatment discontinuation / study withdrawal**: reasons for premature study treatment discontinuation / study withdrawal are identified in the corresponding eCRF modules prefixed with the text “COVID-19 related”, as appropriate (i.e., either for AE, or medical or non-medical reason, whether subject or physician decision).
- **Onset date of adverse events (AEs)**: COVID-19 related AEs are identified if the corresponding preferred terms (PTs) are included in the list as provided in Appendix 2.
- **Date of death**: if the death is COVID-19 related, the primary cause of death should contain the text "COVID-19" in the "Death" eCRF module. (Note: "COVID-19" should then also be reported in the corresponding (S)AE).
- **Protocol deviations (PDs)**: if a PD is linked to COVID-19, the PD term should be prefixed with the text “COVID-19 related”.

Each assessment/visit will be associated to the COVID-19 periods of the pandemic as defined above considering their date respect to the cut-off date of March,11th 2020 (or earlier, as applicable). For example, if the Vital signs assessment was performed before the cut-off date of March,11th 2020, and there is no prior evidence of COVID-19, that assessment is associated to the 'Pre COVID-19' period, otherwise it is associated to the 'During COVID-19' period.

Note that it is possible that 'COVID-19 related' data occurred in the 'Pre COVID-19' period, due to the fact that the study is running since 2014 and the pandemic start date selected for the analyses (11 March 2020) does not necessarily coincide with the COVID-19 virus circulation start date in all centers/countries.

Listing of pandemic start and end dates (based on the definitions above) will be provided per region, country and site for those sites where at least 1 subject was affected. Visit mapping

To minimize the amount of missing data and the possibility to delay the assessments until the on-site visits can be resumed, scheduled visits can be done in remote mode (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and subjects for study procedures e.g. those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent) according to the COVID-19 protocol appendix.

5.2. Subject information

A total of 76 subjects entered MERIT-2, with enrollment activities completed28 Sep 2016. Study Treatment

5.2.1. Disposition

Reasons for premature discontinuation of the study due to COVID-19 are captured in the "Premature study discontinuation" eCRF form.

Reasons for premature study treatment discontinuation due to COVID-19 are captured in the " Premature Permanent Discontinuation of Study Treatment" eCRF form.

The corresponding summaries for study and study treatment disposition as planned in the CSR SAP section 7.1 will show details for subjects who reported reasons for discontinuation due to COVID-19. Therefore, no specific summary will be provided.

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study prematurely due to COVID-19
- Subjects who discontinued study treatment prematurely due to COVID-19.

5.2.2. Extent of Exposure

A subject is considered to have a dose not administered if he/she has a study treatment interruption (i.e., if a reason associated with a study treatment end is ‘Temporarily interrupted due to an AE’ in the "Study Drug Log" eCRF form).

Treatment modifications due to COVID-19 (identifiable from the linked AE) will be listed on the OLAS: temporary study treatment interruptions reported in the "Study Drug Log" eCRF as 'COVID-19 related' AEs with action taken with study drug="Temporarily interrupted" in the 'Adverse Event' eCRF form. A supportive listing will be provided for COVID-19 related AEs

leading to temporarily interruption with action taken with study drug="Temporarily interrupted" in the 'Adverse Event' eCRF form. Additional listing will be provided for these subjects with the study drug dispensed.

5.2.3. Protocol Deviations

COVID-19 related protocol deviations are identified with the text 'COVID-19 related' as a prefix of the PD description.

Subjects with major (see the definition in the CSR SAP, section 8.1) 'COVID-19 related' PDs will be summarized by displaying counts and percentages of subjects with at least one major 'COVID-19 related' PD within each category (as defined in Appendix 4 of the CSR SAP) on OLAS (see table 6 of the CSR SAP) .

All reported 'COVID-19 related' PDs will be described in a subject listing. Major (important) 'COVID-19 related' PDs will be flagged accordingly.

5.2.4. Concomitant Medications

Study treatment concomitant therapies are defined in the CSR SAP (see Appendix 5).

A summary of 'COVID-19 related' medications will be provided on OLAS for subjects who experienced at least one COVID-19 related AE, as specified in Appendix 5 of the CSR SAP.

Those medications reported with an indication for COVID-19 are defined as "COVID-19 related" and contain the words "COVID-19" (including any COVID-19 vaccine that should be reported on the eCRF).

Individual subject's listing of concomitant medications for COVID-19 infection for subjects who experienced at least one COVID-19 related AE will be provided.

5.3. Safety Analyses

All safety analyses and listings will be based on the OLAS, OLSS and RAS analyses sets.

All definitions and conventions used in the CSR SAP Section 8.5 of this study (AC-055E202 /MERIT-2) will be applied, unless otherwise specified.

5.3.1. Adverse Events

COVID-19 related AEs are identified if the corresponding PTs are included in the list as provided in Appendix 2.

Overall summary table of COVID-19 related treatment-emergent AEs will be provided, containing number and percentages of subjects having experienced at least one occurrence and number of AEs for the following categories of TEAEs due to Covid-19:

- Treatment-emergent COVID-19 related AEs
- Severe treatment-emergent COVID-19 related AEs

- COVID-19 related AEs with fatal outcome
- Treatment-emergent serious COVID-19 related AEs (SAEs)
- COVID-19 related AEs leading to premature discontinuation of study treatment

Summary tables by PT will provided for each category defined above.

Summary of overall safety profile will be provided for all AEs by SOC and PT, distinguishing between subjects with and without COVID-19.

In addition, a listing with all COVID-19 related AEs will be provided for subjects who had experienced at least one COVID-19 related AE.

5.3.2. Deaths

A summary table will be provided, containing number and percentages of subjects on the OLAS, OLSS and RAS who died due to COVID-19 during the treatment-emergent period. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died.
- Cause term.
- COVID-19 related cause term.

The summary will be based on the "Death form" eCRF form. The summary will be provided if at least 3 deaths have occurred overall. The summary table is presented by descending order of PT according to the incidence of deaths in the 'Macitentan 10 mg Pool' cohort.

A listing will be provided for subjects who had experienced COVID-19 related death.

5.3.3. Clinical Laboratory Test

The positive results from COVID-19 testing will be captured as COVID-19 related AEs and reported as described in Section 5.3.1 of this document.

Options for the conduct of safety laboratory assessments during the COVID-19 periods of the pandemic (i.e., during COVID-19) are described in the COVID-19 Appendix to Protocol. A summary display will show the percentage of laboratory data (considering all parameters) that were conducted at central and local laboratory during different COVID-19 periods as defined in section 5.3.1 by cohorts defined in section 8.5 of the CSR SAP. This summary output will be presented for all assessments conducted during the course of the study as defined in Table 3 of the SCR SAP.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
COVID	Corona Virus Disease
CSR	Clinical Study Report
eCRF	electronic Case Report Form
PD	Protocol Deviation
PT	Preferred Term
RAS	Restricted Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
OL	Open-Label
OLAS	Open-Label Analysis Set
OLSS	Open-Label Safety Set

6.2. Appendix 2 List of COVID-19 related AEs

AEs are considered as "COVID-19 related" if their coded PTs are:
Asymptomatic COVID-19,
Congenital COVID-19,
Coronavirus infection,
Coronavirus test positive,
COVID-19,
COVID-19 immunization,
COVID-19 pneumonia,
COVID-19 prophylaxis,
COVID-19 treatment,
Exposure to SARS-CoV-2,
Multisystem inflammatory syndrome in children,
Occupational exposure to SARS-CoV-2,
Post-acute COVID-19 syndrome,
SARS-CoV-2 antibody test positive,
SARS-CoV-2 carrier,
SARS-CoV-2 RNA decreased,
SARS-CoV-2 RNA fluctuation,
SARS-CoV-2 RNA increased,
SARS-CoV-2 sepsis,
SARS-CoV-2 test false negative,
SARS-CoV-2 test positive,
SARS-CoV-2 viraemia,
Suspected COVID-19,
Vaccine derived SARS-CoV-2 infection,
Antiviral prophylaxis,
Antiviral treatment,
Coronavirus test,
Coronavirus test negative,
COVID-19 screening,
Exposure to communicable disease,
Pneumonia viral,
SARS-CoV-2 antibody test,
SARS-CoV-2 antibody test negative,
SARS-CoV-2 RNA,
SARS-CoV-2 RNA undetectable,
SARS-CoV-2 test,
SARS-CoV-2 test false positive,
SARS-CoV-2 test negative.