STATISTICAL ANALYSIS PLAN FOR CSR OPEN-LABEL EXTENSION (PATIENTS ENROLLED IN FRANCE)

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PROSPECTIVE, MULTICENTER, PARALLEL GROUP STUDY TO ASSESS THE SAFETY AND EFFICACY OF MACITENTAN IN PATIENTS WITH PORTOPULMONARY HYPERTENSION

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Author	Nicolas Martin, Trial Statistician
Reviewer	Emmanuelle Cottreel, Senior Clinical Scientist
Reviewer	Dmitri Petratchenko, Statistical Programmer
Reviewer	Lada Mitchell, Project Statistician
Reviewer	Loïc Perchenet, Global Post Approval Studies Director

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

AE		Adverse event
ALT		Alanine amino transferase
AST		Aspartate aminotransferase
ATC		Anatomical therapeutic chemical
CSR		Clinical study report
DB		Double-blind
eCRF		Electronic case report form
EOMT		End of macitentan treatment
EOS		End-of-study
EOT		End-of-treatment
EOT-DB		End-of-treatment of the double-blind treatment period
EOT-OL		End-of-treatment of the open-label treatment period
EOT-OLE		End-of-treatment of the open-label extension treatment period
MedDRA		Medical Dictionary for Regulatory Activities
MELD		Model of End-stage Liver Disease
MT		Macitentan
MTS		Macitentan Treated Set
OL		Open-label
OLE		Open-label extension
PAH		Pulmonary arterial hypertension
PAWP		Pulmonary artery wedge pressure
PD		Pharmacodynamic
PDE5i		Phosphodiesterase type 5 inhibitor
PK		Pharmacokinetic
PoPH		Portopulmonary hypertension
PT		Preferred term
PVR		Pulmonary vascular resistance
RHC		Right heart catheterization
SAE		Serious adverse event
SAP		Statistical analysis plan
SAS		Statistical analysis system
SCR		Screened Analysis Set
SDTM		Study Data Tabulation Model

SMQ		Standardised MedDRA Query
SOC		System organ class
SOP		Standard operating procedure
sPAP		Systolic pulmonary arterial pressure
SS		Safety Analysis Set
TPR		Total pulmonary resistance
ULN		Upper limit of the normal range
WHO		World Health Organization
WHODRUG		WHO drug dictionary
WU		Wood units

1 INTRODUCTION

This Statistical Analysis Plan (SAP) "Open-label Extension (OLE)" describes the additional statistical data analyses conducted for the purpose of reporting data collected for the patients enrolled in France that entered into OLE. Data will be reported as clinical study report (CSR) addendum.

These analyses will be performed on the locked database following OLE completion by all patients enrolled in France (who will then have the opportunity to switch to the UMBRELLA study). These analyses will repeat the Macitentan Treated Set (MTS) analyses performed for main CSR but including the OLE phase (cumulative reporting, analysis set named "MTSOLE").

1.1 Study documents

See main study CSR SAP [D-17.045].

2 STUDY DESIGN AND FLOW

See main study CSR SAP [D-17.045].

3 OBJECTIVES

See main study CSR SAP [D-17.045].

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

Not applicable.

4.2 Changes in the conduct of the study / data collection

Not applicable.

4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

Not applicable.

5 DEFINITIONS OF VARIABLES

5.1 Screening failures

Not applicable.

5.2 Subject characteristics

5.2.1 Demographics

Not applicable.

5.2.2 Baseline disease characteristics

Not applicable.

5.2.3 Other baseline characteristics

Not applicable.

5.2.4 Medical history

Not applicable.

5.2.5 Previous and concomitant therapies

5.2.5.1 Previous therapies

Not applicable.

5.2.5.2 Study-concomitant therapies

Not applicable.

5.2.5.3 Study-treatment concomitant therapies

Study-treatment concomitant therapies are any treatment that is either ongoing at the start of macitentan treatment or is initiated during the macitentan treatment period.

Study treatment concomitant therapies are retrieved from the 'Concomitant Medication' and 'Contraceptive Methods' forms of the electronic case report form (eCRF).

5.2.6 Other subject characteristics

Not applicable.

5.3 Study treatment exposure and compliance

5.3.1 Exposure

Study treatment exposure is recorded via the study drug log in the eCRF and retrieved from the Study Data Tabulation Model (SDTM) EX domain. The number of subjects exposed will be displayed per 4-week interval over time. Exposure to study drug will be described in terms of duration in weeks.

The study treatment duration for macitentan treatment period is defined as the number of weeks elapsing between study drug initiation and discontinuation, inclusive, regardless of treatment interruptions and is calculated as:

$$(\text{treatment end date} - \text{treatment start date} + 1) / 7$$

5.3.2 Compliance with study treatment

Not applicable. Reported as part of main study CSR SAP [D-17.045].

5.3.3 Study treatment interruptions

A subject is considered to have had a study treatment interruption if the reason for treatment end is either 'Temporarily interrupted due to an AE [adverse event]' or 'Temporarily interrupted not due to an AE'.

For each period of temporary interruption, the duration of study treatment interruption is determined as:

(treatment restart date – treatment end date – 1)

and summed up per subject.

Treatment exposure in days is determined as the study treatment duration subtracted by the sum of days of treatment interruption.

5.3.4 Premature discontinuation of study treatment

A subject is considered to have prematurely discontinued study treatment if the 'reason for treatment end' in the Study drug Log eCRF is 'Premature Discontinuation'.

5.4 Study discontinuation

Subjects who completed the study as per protocol are those with the question "Did the subject complete the study?" answered "Yes" in the End-of-study (EOS) form of the eCRF.

On the other hand, a subject is considered to have prematurely discontinued the study if the answer to the question "Did the subject complete the study?" in the EOS eCRF is "No".

The date and the reason for End of study are collected in the same form. Withdrawal of consent from study and/or sub-study are also collected.

5.5 Efficacy variables

Not applicable.

5.6 Safety variables

All below statements apply to macitentan treatment emergent period (including OLE).

5.6.1 Adverse events

All below statements apply also to serious AEs.

The MedDRA version used for reporting AEs will be the latest version available at the time of analysis and will be specified as a footnote in the related tables/listings.

5.6.1.1 Treatment-emergent adverse events

Treatment-emergent AEs are defined as those AEs occurring (onset date) during macitentan treatment period for the MTSOLE.

5.6.1.2 Frequency of treatment-emergent adverse events

Treatment-emergent AEs reported more than once within a subject (as qualified by the same preferred term/terms [PTs]) are counted once in the frequency table.

In the event that the reported AE is assigned to several preferred terms, subjects are counted for each individual preferred term.

5.6.1.3 Intensity of treatment-emergent adverse events

For treatment-emergent AEs reported more than once within a subject (as qualified by the same preferred term[s]) within a specified time period but with different intensities, the worst intensity is considered. The categories of intensity are defined as follows:

- Mild
- Moderate
- Severe

If intensity is missing, the event is considered severe.

5.6.1.4 Relationship of treatment-emergent adverse events

Relationship to study treatment is defined as 'related' (yes) or 'not related' (no). For treatment-emergent AEs reported more than once within a subject (as qualified by the same preferred term[s]), the strongest relationship reported [i.e., 'related'] is considered. AEs with missing relationship are considered in any analysis as related.

5.6.2 Deaths

Treatment-emergent AEs with fatal outcome are defined as those AEs occurring during the macitentan treatment period for the MTSOLE. Other deaths occurring outside this time frame, and if collected, will be listed only.

5.6.3 Serious adverse events

A serious adverse event (SAE) is an AE for which the corresponding "Serious?" field in the eCRF AE form is ticked "Yes".

5.6.4 Adverse events leading to discontinuation of study treatment

An AE is defined as leading to discontinuation of study treatment if the corresponding "Action taken with study treatment" field in the eCRF AE form is ticked "Permanently discontinued".

5.6.5 Other significant adverse events

Not applicable.

5.6.6 Physical examinations and vital signs

Not applicable.

5.6.7 Laboratory

Safety laboratory analyses are performed at each visit until End-of-treatment of the open-label extension treatment period (EOT-OLE) and include:

- **Hematology:** hemoglobin, hematocrit, erythrocyte count (reticulocyte count), leukocyte count with differential counts, and platelet count.
- **Blood chemistry:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total and direct bilirubin, gamma-glutamyl transferase, bile acids, creatinine, blood urea nitrogen, uric acid, urea, lactate dehydrogenase, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, protein, and albumin.
- **Coagulation tests (reported with hematology):** prothrombin time, International Normalized Ratio
- **Pregnancy tests:** serum pregnancy test for women of childbearing potential

For the occurrence of post-baseline liver test abnormalities, the following events are considered:

- ALT and /or AST $\geq 3\times$ upper limit of the normal range (ULN),
- ALT and/or AST $\geq 5 \times$ ULN,
- ALT and /or AST $\geq 8 \times$ ULN,
- ALT and /or AST $\geq 3 \times$ ULN and $< 5 \times$ ULN,
- ALT and /or AST $\geq 5 \times$ ULN and $< 8 \times$ ULN,
- ALT and/or AST $\geq 3 \times$ ULN and concomitant (i.e., at the same time) total bilirubin $\geq 2 \times$ ULN.
- ALT and/or AST $\geq 3 \times$ ULN and concomitant (i.e., at the same time) total bilirubin $\geq 2 \times$ ULN (*and* increased as compared to baseline)

The highest ALT or AST value at any post-baseline time point of assessment for macitentan treatment emergent (on MTSOLE) period is considered in the evaluation of incidences.

Treatment-emergent liver test abnormalities are those which occur for macitentan treatment emergent (on MTSOLE) period, that were not present at baseline [see Section 11.1].

For the occurrence of post-baseline hemoglobin abnormalities, the following events are considered in the evaluation of incidences:

- Hemoglobin ≤ 80 g/L,
- Hemoglobin > 80 and ≤ 100 g/L,
- Hemoglobin decrease from baseline ≥ 20 g/L and < 50 g/L,
- Hemoglobin decrease from baseline ≥ 50 g/L,
- Hemoglobin < 100 g/L and concurrent (i.e., at the same time) decrease from baseline ≥ 20 g/L.

The lowest hemoglobin value at any post-baseline time point of assessment for macitentan treatment emergent (on MTSOLE) period is considered in the evaluation of incidences.

Treatment-emergent hemoglobin abnormalities are those which occur for macitentan treatment emergent (on MTSOLE) period, that were not present at baseline [see Section 11.1].

Marked lab abnormalities are defined according to Actelion internal guidelines for individual parameters (same as mentioned main study CSR SAP [D-17.045]).

5.7 Child-Pugh classification and/or MELD Score assessment

Not applicable.

5.8 Pregnancy testing

Not applicable.

5.9 Quality of life variables

Not applicable.

5.10 Pharmacoeconomic variables

Not applicable.

5.11 Pharmacokinetic and pharmacodynamic variables

Not applicable.

6 DEFINITION OF PROTOCOL DEVIATIONS

Not applicable.

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Screened Analysis Set

The Screened Analysis Set (SCR) includes all patients who were screened and received a patient number.

7.1.2 Safety Analysis Set

The Safety Analysis Set (SS) includes all patients who received at least one dose of study treatment in the double-blind (DB) treatment period. Subjects are evaluated according to the actual treatment received.

7.1.3 Other analysis sets

The Macitentan Treated Set OLE (MTSOLE) consists of all patients who received at least one dose of macitentan in the DB or open-label treatment period (including OLE period). The MTSOLE is based on treatment actually received.

7.2 Usage of the analysis sets

Summaries of safety data will be performed on the MTSOLE.

Patient listings will be based on the SCR, except listings of exposure data that will be based on SS.

8 DEFINITION OF SUBGROUPS

Not applicable.

9 GENERAL STATISTICAL METHODOLOGY

SAS (Statistical Analysis System®) version 9.3 or higher will be used for all the statistical analysis.

Data are listed and summarized by appropriate descriptive statistics (tables or figures), typically including:

- Number of non-missing observations, mean, standard deviation, minimum, Q1, median, Q3, and maximum for continuous variables,
- Number of non-missing observations, frequency with percentage per category (percentages based on the number of non-missing observations) for categorical safety variables,
- Number of missing observations and frequency with percentage per category (percentages based on the total number of observations) for categorical variables other than safety variables.

The number of missing values is displayed only if > 0. For continuous variables it is displayed after the number of non-missing observations, for categorical variables after the last category.

Absolute changes from baseline are defined as: post-baseline value minus the baseline value, such that a positive sign indicates an increase compared to baseline.

10 STATISTICAL ANALYSES

10.1 Overall testing strategy

Not applicable.

10.2 General rules for data presentation

General rules for data presentation, as described below, are to be followed unless otherwise specified.

In general, data are listed and summarized by appropriate descriptive statistics (tables or figures) as described in the previous section.

Listings are grouped by treatment arm (beginning with macitentan 10 mg and, if applicable, screen failures are listed last), country, site, subject number, and assessment date as applicable.

Raw data listings if required are based on datasets as received. All data collected are displayed, including unscheduled visits (if any).

10.3 Display of subject disposition, protocol deviations and analysis sets

10.3.1 Subject disposition

Not applicable.

10.3.2 Protocol deviations

Not applicable.

10.3.3 Analysis sets

The analysis set MTSOLE will be based on same patients as MTS in main analysis but including data from OLE in a cumulative way.

10.4 Analyses of subject characteristics

10.4.1 Disposition of patients

Not applicable.

10.4.2 Demographics

Not applicable.

10.4.3 Baseline disease characteristics

Not applicable.

10.4.4 Medical history

Not applicable.

10.4.5 Previous and concomitant therapies

Previous and concomitant therapies are classified according to the anatomic therapeutic chemical (ATC) class code and will be summarized by tabulating the number and percentages of subjects having received treatment using the MTSOLE.

Study-treatment concomitant therapies will be summarized by ATC class and PT.

For study reporting purposes, all previous and study-concomitant therapies will be reported in the subject listings. It will be indicated if the therapy is previous or concomitant.

10.5 Analysis of study treatment exposure and compliance

10.5.1 Exposure (weeks)

The exposure time will be summarized for the Macitentan treatment period on MTSOLE, using descriptive statistics. It will also be summarized as categorical variable: the cumulative distribution of exposure time by different class intervals will be tabulated to show counts and percentages of patients in each class interval.

10.5.2 Compliance with study treatment

Not applicable.

10.5.3 Study treatment interruptions

The study treatment interruptions defined in Section 5.3.3 will be listed and summarized per treatment group using descriptive statistics for categorical data.

Frequency tables will be presented displaying the number of subjects with at least one interruption and the reasons from the study drug log eCRF page “Temporarily interrupted due to an AE” and/or “Temporarily interrupted not due to an AE”. The numbers in the categories may total a number greater than the number of subjects with an interruption, as a single subject could have multiple interruptions for multiple reasons.

Percentages of subjects with at least one interruption of study drug intake for more than 7, 14, and 21 days will be displayed. These counts will be “cumulative”, i.e., if a subject interrupts treatment for more than 21 days, they are counted in all three categories: “more than 7 days”, “more than 14 days”, “more than 21 days”.

The total duration of study treatment interruption will be summarized using descriptive statistics for continuous data.

Analyses will be performed for the Macitentan open-label treatment period on the MTSOLE.

10.5.4 Study treatment discontinuation

The proportion and number of patients having permanently discontinued study treatment will be provided for each treatment period. The cause for permanent discontinuation will be tabulated as frequency and percentage for the Macitentan open-label treatment period on MTSOLE.

10.6 Study discontinuation

Study discontinuation [see Section 5.4] reporting is conducted as part of the subjectdisposition described in Section 10.3.1. Reasons for study discontinuation will be reported in a subject listing for the SCR.

10.7 Analysis of the primary efficacy variable

Not applicable.

10.8 Analysis of the secondary efficacy variables

Not applicable.

10.9 Analysis of other efficacy variables

Not applicable.

10.10 Analysis of safety variables

All safety analyses will be performed for MTSOLE.

All safety data will be included in the listings, with flags for treatment emergency and quantitative abnormalities, where appropriate.

10.10.1 Adverse events

The number and percentage of patients experiencing treatment emergent AEs and SAEs will be tabulated for macitentan treatment emergent (on MTSOLE) period and by:

- MedDRA System organ class (SOC) and individual preferred term within each SOC, in descending order of incidence.
- Frequency of patients with events coded with the same PT, in descending order of incidence.

Furthermore, treatment-emergent AEs for macitentan treatment emergent (on MTSOLE) period will be tabulated by severity and relationship to the study drug, as described above.

AEs leading to premature discontinuation of the study treatment and death will also be summarized as described above.

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

10.10.2 Deaths, other serious adverse events

10.10.2.1 Death

Treatment-emergent deaths for macitentan treatment emergent (on MTSOLE) period will be tabulated as described in Section 10.10.1, overall and by cause.

Death, along with the cause, will also be listed from Screening to EOS.

10.10.2.2 Serious adverse events

Treatment emergent SAEs for macitentan treatment emergent (on MTSOLE) period will be tabulated as described in Section 10.10.1. SAEs from Screening to EOS will also be listed.

10.10.2.3 Adverse events leading to study treatment discontinuations or death

AEs leading to premature discontinuation of study treatment will also be summarized as described above.

10.10.2.4 Other significant adverse events

In addition, following AEs of special interest will be reported for macitentan treatment emergent (on MTSOLE) period:

- *"Edema and fluid retention"*

Any treatment-emergent AE with PT listed in the Standardised 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 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".

- *"Drug related hepatic disorders"*

Any treatment-emergent AE with a PT within the SMQ "Drug related hepatic disorders"

10.10.3 Electrocardiogram

Not applicable.

10.10.4 Laboratory tests

All hematology and chemistry variables provided by the central and local laboratory will be provided in a subject listing. Marked laboratory abnormalities will be flagged accordingly. All laboratory data transferred will be taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

If laboratory test results are given by threshold values ('< x' or '> x'), the threshold values will be considered for quantitative analysis.

Laboratory data will be presented in standard international units.

Descriptive summary statistics by visit and study treatment are displayed for observed values and absolute changes from baseline to each time point for hematology and blood chemistry laboratory tests from the central laboratory. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments from the central laboratory up to EOS will be assigned to the most appropriate visit time point according to the best fitting time window for the assessment.

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

Treatment-emergent marked laboratory abnormalities (see main study CSR SAP [D-17.045]) will be summarized for macitentan treatment-emergent (on MTSOLE) period for each laboratory parameter providing their incidence, frequency, and number of subjects with the available assessments.

Percentages will be calculated as the number of subjects who had at least one occurrence of the abnormality, for the variable under consideration divided by the number of subjects with any post-baseline laboratory measurement.

Shift tables will be used to summarize the worst treatment-emergent laboratory abnormalities, based on the definition of marked laboratory test abnormalities. The worst category will be taken for the analysis for each direction.

If HH, HHH, LL or LLL is not defined for a variable, "NA" will appear in the table for the corresponding variable. Percentages are calculated based on the number of subjects in the analysis set.

Separate tables with the incidence of liver test abnormalities and hemoglobin abnormalities will be produced including summaries on the criteria as defined in Section 5.6.7.

10.10.5 Vital signs and body weight

Not applicable.

10.10.6 Child-Pugh score and MELD score

Not applicable.

10.10.7 Other safety variables

Not applicable.

10.11 Analysis of quality of life variables

Not applicable.

10.12 Analysis of pharmacoeconomic variables

Not applicable.

10.13 Analysis of epidemiological measures and risk-benefit evaluations

Not applicable.

10.14 Analysis of pharmacodynamic variables

Not applicable.

10.15 Analysis of pharmacokinetic variables

Not applicable.

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Baseline assessment

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 (DB period).

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

- patients who received macitentan already in the DB period, macitentan baseline is the last available assessment performed on or prior to DB period start date.
- patients who received macitentan only in the open-label period, macitentan baseline is the last available assessment performed on or prior to open-label period start date.

11.2 Post-baseline assessment

Post-baseline assessment is any assessment performed after baseline and up to EOS.

11.3 Study day

This is the number of days elapsed since the day of randomization + 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 the randomization date. Therefore, the study day is always different from 0.

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

- patients who received macitentan already in the DB period, the MT day is the number of days elapsed since the day of randomization + 1 (as randomization is considered Day 1).
- patients who received macitentan only in the open-label period, the MT day is the number of days elapsed since the OL start date + 1 (as OL start date is considered MT Day 1).

11.4 Randomization date

This is the date of the interactive voice/web recognition system form of the eCRF.

11.5 Double-blind period start date

It is the first day of intake of study treatment during the DB period. It is derived from the first treatment start date (in chronological order) in the Study Drug Log eCRF, where the 'Study Period' is given as the 'DOUBLE-BLIND STUDY DRUG'. If missing, the *Randomization date* will be used.

11.6 Double-blind period end date

This is the 'Treatment-end date' from the last interval, in chronological order, recorded in the study drug log eCRF, where the 'Study Period' is 'DOUBLE-BLIND STUDY DRUG' and the reason for treatment end is ≠ 'TEMPORARILY INTERRUPTED DUE TO AN AE' or 'TEMPORARILY INTERRUPTED NOT DUE TO AN AE'. If missing or incomplete, rules in Section 12 are to be followed according to Table 3.

The DB period is the period from the start up to End of the DB treatment (EOT-DB; limits included).

11.7 Open-label period start date

It is the first day of intake of study treatment during the open-label period. It is derived from the first treatment start date (in chronological order) in the Study Drug Log eCRF, where the 'Study Period' is given as the 'OPEN-LABEL STUDY DRUG'.

11.8 Open-label period end date

This is the 'Treatment end date' from the last interval, in chronological order, recorded in the study drug log eCRF, where the 'Study Period' is 'OPEN-LABEL STUDY DRUG'. If missing or incomplete, rules in Section 12 are to be followed according to Table 3.

The open-label period is the period from the start up to end of open-label (limits included).

11.9 Open-label extension period start date

It starts immediately after EOT-OL for those subjects randomized at the French sites who have completed the core phase of the study as scheduled and opt to continue receiving OL study treatment. It is derived from the first treatment start date (in chronological order) in the Study Drug Log eCRF, where the 'Study Period' is given as the 'OPEN-LABEL EXTENSION STUDY DRUG'.

11.10 Open-label extension period end date

This is the "Treatment end date" from the last interval, in chronological order, recorded in the study drug log eCRF, where the 'Study Period' is given as 'OPEN-LABEL EXTENSION STUDY DRUG'. If missing or incomplete, rules in Section 12 are to be followed according to Table 3.

The open-label extension period is the period from the start up to end of open-label extension (limits included).

11.11 End-of-Study date

This is the date of the "End of Study" form of the eCRF.

11.12 Double-Blind treatment-emergent period (for safety variables reporting)

The DB treatment-emergent period is defined as the period from the DB treatment start date up to the DB treatment end date + 30 days or to the DB treatment end date [see definition in Section 11.7] for patients entering OL.

For laboratory, vital signs, and body weight, Child-Pugh score and Model of End-stage Liver Disease (MELD) score analyses, the DB treatment-emergent period defined above starts from the DB treatment start date excluded.

11.13 Macitentan treatment-emergent period (for safety variables reporting)

The macitentan treatment-emergent period is defined as the period from the first intake of macitentan up to End of macitentan treatment (EOMT) + 30 days (including OLE). EOMT is defined as EOT-DB (for the patients who received macitentan only in the DB period) or EOT-OL/EOT-OLE where applicable, whichever comes last.

Important: for patients switching to the UMBRELLA study, the end of macitentan treatment-emergent period will be the EOT-OLE.

For laboratory, vital signs, and body weight, Child-Pugh score and MELD score analyses, the macitentan treatment-emergent period defined above starts from the first intake of macitentan excluded.

- Note: for reporting purpose, in the exceptional situation that the end date of a period is equal to the start date of the next period (for example the end date of OL period is

equal to the start date of OLE period), the 'event' is associated with the first of the two periods (in this example, it is associated with the start of the OL study).

11.14 Time windows

In order to minimize missing data and to analyze the efficacy and safety data at the relevant planned (scheduled) visits, all recorded assessments for each subject are to be reassigned to the most appropriate visit according to the best fitting time window for that visit. Any unscheduled visit will also be mapped to a time window. The windows are based on the number of study days, corresponding to the date of assessment recording - see Table 1 for the DB period and the MTSOLE analyses of subjects who had already received macitentan in the DB period and Table 2 or the MTSOLE analyses for subjects who first received macitentan in the open-label period.

Should more than one assessment fall within the same time window, then the closest value to the planned time point (nominal value) will be assigned for presentation in data summaries and analyses. In the event of values that are equidistant to the planned time point, the later assessment will be considered for the analyses. If more than one value falls on the same timepoint then the one with the last sequential number in SDTM will be used.

Programming note: values that are not retained for presentation in summaries per visit should be kept in the datasets and used as appropriate when applying substitution rules for missing data.

Individual data listings consider all data by nominal visit identifier with data flagged if considered for time windows.

Table 1 Visit time windows (for the double-blind period analysis and the MTSOLE analyses of subjects who received macitentan already in the double-blind period)

Mapping of all visits to:	**Treatment day (nominal value)**	**Lower limit Treatment day**	**Upper limit Treatment day**
Baseline	Day 1	No limit	1
Week 4	Day 28	2	42
Week 8	Day 56	43	70
Week 12	Day 84	71	98
Week 16	Day 112	99	126
Week 20	Day 140	127	154
Week 24	Day 168	155	182
Week X	**Day X*7**	**(X*7) - 13**	**(X*7) + 14**

Table 2 Visits time windows (for the MTSOLE analyses of subjects who received macitentan only in the open-label period)

Mapping of all visits to:	MT treatment day (nominal value)	Lower limit MT treatment day	Upper limit MT treatment day
Baseline	MT Day 1	No limit	1
Week 4	MT Day 28	2	42
Week 8	MT Day 56	43	70
Week 12	MT Day 84	71	98
Week X	**Day X*7**	**(X*7) - 13**	**(X*7) + 14**

12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

All dates and times used in the analyses are supposed to be complete, apart from the types included in the table below.

Missing or incomplete dates are handled as follows:

- Dates are split into three parts: year, month and day. Year is the top level, month is medium level and day is low level. If a part that is 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.
- If a part that is expected to contain a number is not numeric, i.e., contains values like such as ND, NA, --, ??, 2?, it is considered to be missing.
- If a part is missing, all lower level parts are considered to be missing. This means that a ddmmyy date '21ND99' is considered as '----99'.

Missing parts for specific dates/times are changed into acceptable non-missing values depending on the type of date to be replaced.

In Table 3, 'lower limit' and 'upper limit' refer to the minimum or maximum of a possible date. As an example, if only 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.

Table 3 Types of missing or incomplete date/time fields

Type of date/time	Date/time is incomplete	Date/time is missing
AE resolution date	The upper limit	No replacement, the AE is considered as ongoing in the analysis
AE onset date	If the end date of the AE is not before the study treatment start date (DB period), and if the study treatment start falls in the range of possible dates, the study treatment start date is used. In all the other cases, the lower limit is used.	The earlier of the date of resolution of the AE and the study treatment start date (DB period)
Previous/ concomitant therapy start date	Lower limit except when: Not tagged as ongoing at start of treatment AND Therapy end date not collected or with the upper limit after the study treatment start date AND The study treatment start day falls in the range of possible dates. In which case it is the study treatment start day	No replacement, the therapy is considered to have started before the study

Type of date/time	Date/time is incomplete	Date/time is missing
Previous/ concomitant therapy end date	Upper limit except when: Therapy start is before study treatment start (DB) or missing AND Upper limit is after the study treatment start (DB) AND Not tagged as ongoing at start of treatment. In which case it is 1 day before study treatment start	No replacement (considered ongoing)
Date of PAH/PoPH diagnosis	Day missing: 15th of the month Day and month missing: 30th of June If the resulting date is later than the date of randomization and the lower limit is not later than the randomization date, then the date is substituted with the date of randomization.	No replacement
EOS	Upper limit	Final database-lock date
EOT-DB	Use the earliest date between the: Start of OL −1 day Upper limit EOS Date of death	Use the earliest date between the: Start of OL −1 day EOS Date of death

Type of date/time	Date/time is incomplete	Date/time is missing
EOT-OL	Use the earliest date between the: Start of OLE −1 day (where applicable) Upper limit EOS Date of death	Use the earliest date between the: Start of OLE −1 day (where applicable) EOS Date of death
EOT-OLE	Use the earliest date between the: Upper limit EOS Date of death	Use the earliest date between the: EOS Date of death
Death date	Use the lower limit	No replacement

AE = adverse event, DB = double-blind, OLE = open-label extension, EOS = End-of-study, EOT-DB = End-of-treatment of the double-blind treatment period, EOT-OL = End-of-treatment of the open--label treatment period, EOT-OLE = End-of-treatment of the open--label extension treatment period, PAH = pulmonary arterial hypertension, PoPH = portopulmonary hypertension.

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

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

The table, listing, and figure naming conventions have three components: ***Type*** (T, L, or F), ***Name*** (free text, no longer than ten characters), ***Suffix*** (for example, for analysis sets, or subgroups, no longer than four characters). Multiple suffixes can be added; components/suffixes are separated by an underscore '_'.

Key deliverables are marked as being of priority.

Mock layouts refer to specifications in the AC-055-404 layouts for TLFs [Tables, Listings, and Figures] document.

13.1 Subject disposition

Not applicable.

13.2 Protocol deviations

Not applicable.

13.3 Subject characteristics

13.3.1 Demographics

Not applicable.

13.3.2 Baseline disease characteristics

Not applicable.

13.3.3 Medical history

Not applicable.

13.4 Previous and concomitant therapies

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
CTTATCPR	T	Study-treatment concomitant therapies by anatomic therapeutic chemical class (ATC) and preferred term	MTSOLE		TS10
PCTHER	L	Listing of subjects with previous and concomitant therapies	SCR		LS11

* L = Listing, T = Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR = Screened Analysis Set.

13.4.1 Other subject characteristics

Not applicable.

13.5 Study treatment exposure and compliance

13.5.1 Exposure

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
TREXP	T	Study treatment exposure	MTSOLE		TS11
TREXP	L	Listing of exposure	SS		LS13

* L = Listing, T= Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SS = Safety Analysis Set.

13.5.2 Compliance with study treatment

Not applicable.

13.5.3 Study treatment interruptions

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
STI	T	Study treatment interruptions	MTSOLE		TS14
STI	L	Listing of study treatment interruptions	SCR		LS16

* L = Listing, T = Summary table, ** SCR = Screened analysis set, MTSOLE = Macitentan Open-label Extension Treated Set

13.5.4 Study treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PDISCTR	T	Reasons for premature discontinuation of study treatment	MTSOLE		TS13

* T = Summary table ** MTSOLE = Macitentan Open-label Extension Treated Set

13.6 Study discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PDISCST	T	Reasons for premature study discontinuation	MTSOLE		TS15
PDISC	L	Listing of discontinued subjects	SCR		LS17

* L = Listing, T = Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR = Screened Analysis Set.

13.7 Primary efficacy analyses

Not applicable.

13.8 Secondary efficacy analyses

Not applicable.

13.9 Safety analyses

13.9.1 Adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEOV	T	Overview of treatment-emergent adverse events (AE)	MTSOLE		TS33
AESCPR	T	Treatment-emergent adverse events (AE) by system organ class (SOC) and preferred term	MTSOLE		TS34
AEPR	T	Treatment-emergent adverse events (AE) by preferred term	MTSOLE		TS35
AEPRIN	T	Treatment-emergent adverse events (AE) by maximum intensity and preferred term	MTSOLE		TS36
AERESCPR	T	Treatment-emergent adverse events (AE) related to study treatment by system organ class (SOC) and preferred term	MTSOLE		TS34
AE	L	Listing of adverse events (AE)	SCR		LS23

* T = Summary table, L = Listing ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR = Screened Analysis Set.

13.9.2 Deaths

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEFASCPR	T	Treatment-emergent adverse events (AE) with fatal outcome by system organ class (SOC) and preferred term	MTSOLE		TS34
DEAPR	T	Cause of death	MTSOLE		TS37
DEATH	L	Listing of deaths	SCR		LS24

* L = Listing T = Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR = Screened Analysis Set.

13.9.3 Serious adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SAESCPR	T	Treatment-emergent serious adverse events (SAE) by system organ class (SOC) and preferred term	MTSOLE		TS34
SAE	L	Listing of serious adverse events (SAE)	SCR		LS23

* L = Listing, T = Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR = Screened Analysis Set.

13.9.4 Adverse events leading to treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AEPDSCPR	T	Adverse events (AE) leading to premature discontinuation of study treatment by system organ class (SOC) and preferred term	MTSOLE		TS34
AEPD	L	Listing of adverse events (AE) leading to premature discontinuation of study treatment	SCR		LS23

* L = Listing, T = Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR = Screened Analysis Set.

13.9.5 Other significant adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AESISCPR	T	Treatment-emergent adverse events of special interest (AE) by system organ class (SOC) and preferred term	MTSOLE		TS34
NSAESFCPRE	T	Occurrence of non-serious frequent (≥5%) treatment-emergent adverse events (AE)	MTSOLE		TS38
SAESCPRE	T	Occurrence of treatment-emergent serious adverse events (SAE)	MTSOLE		TS38

* T=Summary table** MTSOLE = Macitentan Open-label Extension Treated Set

13.10 Laboratory tests

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABCGTPHEM	T	Hematology: Change in laboratory tests from baseline to each timepoint	MTSOLE		TS40
LABCGTPBCH	T	Chemistry: Change in laboratory tests from baseline to each timepoint	MTSOLE		TS40
LABMLAHEM	T	Hematology: Marked laboratory abnormalities	MTSOLE		TS41
LABMLABCH	T	Chemistry: Marked laboratory abnormalities	MTSOLE		TS41
LABLHLA	T	Liver and hemoglobin laboratory abnormalities	MTSOLE		TS42
LABSHHEMLOW	T	Hematology: Shift in laboratory tests from baseline to the worst low value	MTSOLE		TS43
LABSHHEMHIGH	T	Hematology: Shift in laboratory tests from baseline to the worst high value	MTSOLE		TS43
LABSHBCHLOW	T	Chemistry: Shift in laboratory tests from baseline to the worst low value	MTSOLE		TS43
LABSHBCHHIGH	T	Chemistry: Shift in laboratory tests from baseline to the worst high value	MTSOLE		TS43
LABSI	L	Listing of individual laboratory measurements (SI units)	SCR		LS25

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LABORIG	L	Listing of individual laboratory measurements (original units)	SCR		LS25
LABLMA	L	Listing of individual laboratory measurements (subjects with at least one marked abnormality)	SCR		LS26

* L= Listing, T=Summary table. ** MTSOLE = Macitentan Open-label Extension Treated Set, SCR=Screened Analysis Set.

13.11 Vital signs and body weight

Not applicable.

13.12 Other safety variables

Not applicable.

13.13 Other safety variables

Not applicable.

13.14 Other evaluations

13.14.1 PK sub-study

Not applicable.

14 REFERENCES

[D-17.045] A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension. Actelion Pharmaceuticals Ltd; Clinical Study Report SAP for AC-055-404, 6 February 2018.

15 APPENDICES

Appendix 1 Document history

Summarize the main changes and rationale for changes from one approved version to the next.

Version	Effective Date	Reason
1.0	7 Aug 2018	Initial final version
2.0	17 Oct 2018	Addition of a table for adverse events of special interest and for disclosure.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd HH:mm)
Dmitri Petratchenko	Clinical Approval	2018-10-17 13:16 GMT+020
Nicolas Martin	Clinical Approval	2018-10-17 13:26 GMT+020
Lada Mitchell	Clinical Approval	2018-10-17 13:32 GMT+020
Loic Perchenet	Clinical Approval	2018-10-17 13:41 GMT+020
Emmanuelle Cottreel	Clinical Approval	2018-10-17 16:08 GMT+020