NCT03775421

Janssen Research & Development

Statistical Analysis Plan

Prospective, multi-center, single-arm, open-label long-term study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects

AC-055H302/RUBATO-OL; Phase 3

ACT-064992 / JNJ-67896062 (macitentan)

Status:	Approved
Date:	17 December 2021
Prepared by:	Actelion Pharmaceuticals Ltd., a Janssen Pharmaceutical Company of Johnson & Johnson
Document No.:	EDMS-RIM-265704, 1.0

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

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	17 December 2021	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the methods, conduct and content of the data analysis of AC-055H302/RUBATO open-label extension study (hereafter referred to as the RUBATO OL study) for the purpose of the abbreviated Clinical Study Report (CSR). As planned in the protocol, some of the analyses are based on data pooled with data from the corresponding core study, AC-055H301/RUBATO (hereafter referred to as the RUBATO DB study).

Following the evaluation of the study results from the RUBATO DB study, a sponsor decision was taken to terminate the RUBATO OL study early. For this reason, an abbreviated CSR is planned. All safety data and selected non-safety data obtained will be summarized in the abbreviated CSR.

All analyses are exploratory in nature and therefore no multiplicity issues are foreseen.

This SAP refers to the documents listed in Table 2.

Table 2: Study Documents

Document	Date, Version
Study Protocol AC-055H302 (RUBATO OL)	Final Version 4 (D-20.426)
Study Protocol AC-055H301 (RUBATO)	Final Version 10 (D-20.425)
AC-055H301 SAP for clinical study report (CSR)	Final Version 5 (EDMS-RIM-264216, 3.0)
AC-055H301 SDTM annotated eCRF specifications	Version 1.0, 8 September 2021, or latest implemented version
AC-055H302 SDTM annotated eCRF specifications	Version 11.0 (draft 19 October 2021), or latest implemented version
Study Protocol AC-055H302 (RUBATO OL) COVID-19 Appendix	Approved version, 17 June 2020 (D-20.159)
Study Protocol AC-055H301 (RUBATO) COVID-19 Appendix	Approved version, 17 June 2020 (D-20.158)

Source data for the AC-055H301/RUBATO DB will be Analysis Data Model (ADaM) data sets derived for the AC-055H301/RUBATO CSR SAP. Except where otherwise specified, all definitions and conventions used in the CSR SAP of this study will be applied, as applicable.

Source data for the RUBATO OL study are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM). Source data are provided according to the Database Release Plan document.

The pooling of RUBATO DB and RUBATO OL means that the data from the same subjects randomized in RUBATO DB will be concatenated with their data from the OL study. The concatenation of data from the same subject is referred to as ‘pooling’ in this document.

1.1. Objectives and Endpoints

The primary objective of the study is to assess the long-term safety and tolerability of macitentan in Fontan-palliated adult and adolescent subjects. This SAP describes how safety and selected

efficacy will be analyzed and summarized in order to support the abbreviated RUBATO OL CSR. This includes the concatenation of data from studies RUBATO DB and RUBATO OL.

1.2. Study Designs

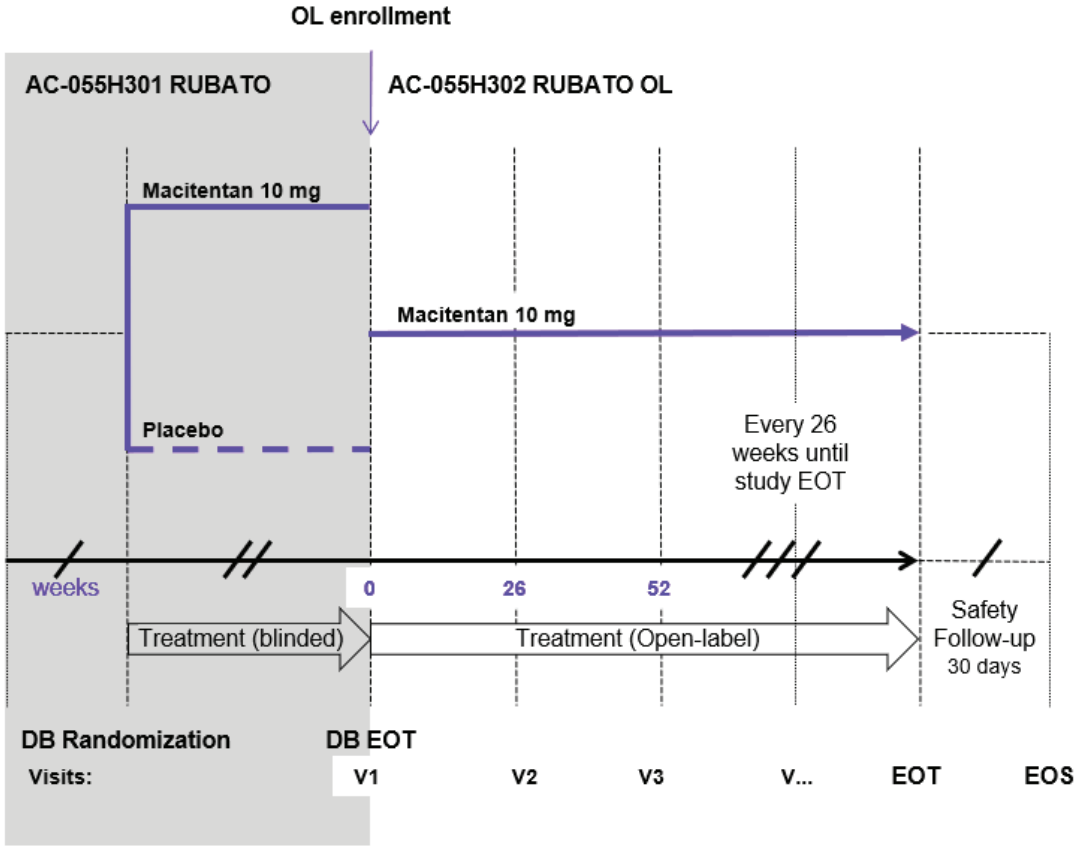
RUBATO DB is a prospective, multi-center, double-blind, randomized, placebo controlled, parallel-group Phase 3 study assessing the efficacy and safety of macitentan in Fontan-palliated adult and adolescent subjects.

At least 134 subjects were to be randomized in a 1:1 ratio to receive 52 weeks of treatment with either macitentan or placebo. Randomization was stratified by geographical region (America, Europe, Asia, Oceania). The study was to be conducted in approximately 31 investigational sites in 11 countries.

The study is completed, database was locked on 02-Sep-2021.

RUBATO OL is a prospective, multi-center, single-arm, open-label, long-term, Phase 3 study assessing the safety, tolerability, and effectiveness of macitentan in Fontan-palliated adult and adolescent subjects. The overall study design of RUBATO OL is depicted in Figure 1.

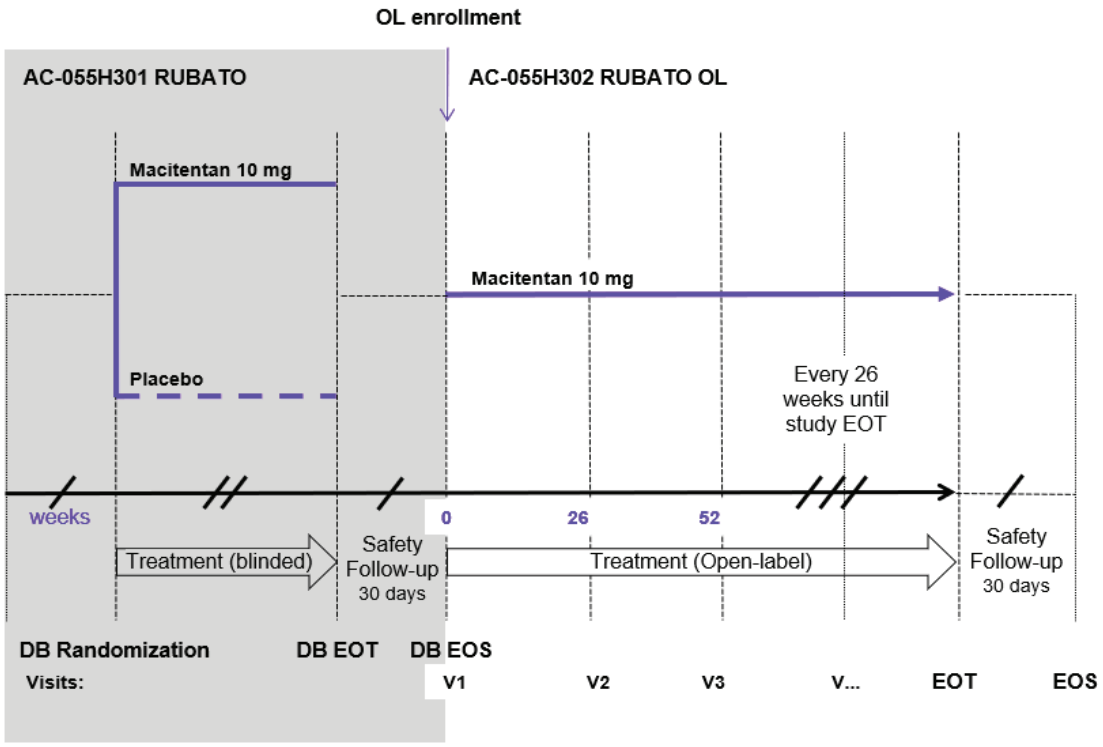
Figure 1: RUBATO OL Study Design



DB = Double-blind (study); EOS = End-of-Study; EOT = End-of-Treatment; OL = Open-label (extension); V = visit
☎= Telephone call (for visit).

In instances where administration of RUBATO OL study treatment does not immediately follow End-of-Treatment (EOT) in the RUBATO DB study, the subject will enter the DB S-FU period per protocol until administration of the first dose of the OL study treatment occurs (Figure 2).

Figure 2: RUBATO OL Study Design (with S-FU in the AC-055H301 RUBATO DB Study)



DB = Double-blind (study); EOS = End-of-Study; EOT = End-of-Treatment; OL = Open-label (extension); S-FU = Safety Follow-up; V = visit; ☎= Telephone call (for visit).

No S-FU will be performed for subjects entering a post-trial access program at individual subject's EOT for the RUBATO OL study.

Visit and assessment schedules of the RUBATO DB and the RUBATO OL studies can be found in the corresponding protocols.

As it was recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of the clinical studies, the sponsor issued Study Protocol COVID-19 Appendices to provide options for study related subject management in the event of disruption to the conduct of the study. Discontinuations of study interventions and withdrawal from the study were to be documented with the prefix "COVID-19-related" in the electronic case report form (eCRF). Also, protocol deviations (PDs) linked to COVID-19, were to be prefixed with the text "COVID-19 related" in the clinical database.

The RUBATO DB results showed no clinically meaningful difference favoring macitentan 10 mg that would provide treatment benefit to Fontan-palliated patients, and therefore, the sponsor has decided that the RUBATO OL study will be terminated early.

2. STATISTICAL HYPOTHESES

No formal hypothesis testing is performed. All efficacy analyses are purely descriptive.

3. SAMPLE SIZE DETERMINATION

Not applicable. RUBATO OL is an extension study of the RUBATO DB study, hence the sample size of the pools will be up to the number of randomized subjects in the RUBATO DB study, with no sample size statistical considerations.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Table 3 below describes analysis sets, periods and treatment arms used.

Table 3: Analysis Set Definitions

Analysis Set	Period definition	Treatment Arms
RUBATO Open-label Extension Set (OLES)	The RUBATO Open-label Extension Set (OLES) includes all subjects treated with macitentan in RUBATO OL study. Only data from the OL period (as defined in Section 5.1.2.6) are considered with the exception of baseline data (including demographic data, medical and disease history data, prior medication) which may origin from the DB period. Treatment arms "DB-Macitentan 10 mg" and "DB-Placebo" follow the treatment arm from RUBATO DB safety set (SS), i.e., are based on actual treatment received in study RUBATO DB.	DB-Placebo DB-Macitentan 10 mg OL Macitentan 10 mg (All OLES subjects)
RUBATO pool (FAS and SS)	Pool of all RUBATO DB and RUBATO OL data. Data from the same subjects randomized in DB are concatenated with their data from the OL extension study. Baseline is defined relative to first intake of study medication in the RUBATO DB study, as defined in the RUBATO DB study SAP. Treatment arms for FAS follow the treatment arm assignment from RUBATO DB FAS analyses, i.e., treatment as randomized. Treatment arms for SS follow the treatment arm assignment from RUBATO DB SS analyses, i.e., are based on actual treatment received in study RUBATO DB.	Placebo/Macitentan 10 mg (Plc/Maci) Macitentan 10 mg /Macitentan 10 mg (Maci/Maci)
RUBATO Total Macitentan Analysis Set (TMAS) (SS)	Only subjects receiving at least one dose of macitentan (either in RUBATO DB or RUBATO OL) are included. Only subjects from the macitentan arm in the RUBATO DB SS analyses are considered to have received macitentan in the RUBATO DB, their data are concatenated with their data from the OL extension. For subjects from the DB study SS placebo arm, only data with assessment dates during the OL period (as defined in in Section 5.1.2.6) are considered, with the exception of baseline data (including demographic data, medical and disease history data, prior medication) which may origin from the DB period. Baseline is defined relative to first intake of macitentan study treatment (either in RUBATO DB or RUBATO OL).	Macitentan 10 mg Pool

FAS – Full analysis set, SS – Safety Set.

Table 4 describes usage of analysis sets.

Table 4: Usage of Analysis Sets

	Analysis Set		
Endpoint	**RUBATO OLES**	**RUBATO pool**	**RUBATO TMAS (SS)**
Efficacy			
CPET (peak VO_2, VO_2 at VAT)	Yes	Yes (FAS)	
PA-Ac (Mean count per minute)	Yes	Yes (FAS)	
Fontan-palliated clinical worsening		Yes (FAS)	
Fontan-palliated morbidity		Yes (FAS)	
Safety			
AEs (incl SAEs, AESI, AE by intensity, by relationship, AE leading to study treatment discontinuation, fatal AEs)	Yes	Yes (SS) for Maci/Maci Arm only	Yes
Death		Yes (SS)	
Vital signs (BP, pulse) including peripheral oxygen saturation (SpO_2) and body weight, over time	Yes	Yes (SS)	
Systolic blood pressure outlier analyses	Yes	Yes (SS) for Maci/Maci Arm only	Yes
Laboratory results, over time	Yes	Yes (SS)	
Marked laboratory abnormalities/laboratory outlier analyses	Yes	Yes (SS) for Maci/Maci Arm only	Yes
Echocardiography numerical results, over time	Yes	Yes (SS)	
Echocardiography valvular defects	Yes	Yes (SS)	Yes
Exposure/Compliance	Yes	Yes (SS)	Yes
Demographics	Yes		Yes
Baseline Disease Characteristics	Yes		Yes
Disposition	Yes		Yes
Protocol Deviations	Yes		
Concomitant Medications	Yes		Yes

5. STATISTICAL ANALYSES

5.1. General Considerations

SAS (Statistical Analysis System®) version 9.4 is used for all the statistical analyses, except if otherwise specified.

Data will be listed and summarized by appropriate descriptive statistics (tables or figures).

General rules for data presentations as described below are followed unless otherwise specified:

- All listings will be sorted by treatment arm, site ID, subject ID and when appropriate by visit / date of assessment. All data collected will be displayed, including unscheduled visits (if any).
- In summary tables, treatment arms will be presented in columns from left to right following the order shown in Table 3.
- If on a table or figure a visit/timepoint is empty (i.e., zero subjects across all treatment arms), this visit/timepoint is not displayed.

5.1.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits.

Visit-based analyses are planned to be conducted based on the RUBATO OLES and on the RUBATO pool. Analysis visits for the RUBATO DB period within the RUBATO pool follow the RUBATO DB SAP, visits labelled “Baseline” or “Week xx” in the RUBATO DB CSR SAP are re-labelled to “DB Baseline” or “DB Week xx”. For the RUBATO OL period, analyses visits are assigned according to Table 5.

Safety assessments are generally reported based on the nominal visit, i.e., according to the visit reported in the database, however for subjects who discontinued OL study treatment prematurely with available premature EOT visit, the EOT assessments may be re-assigned to a scheduled visit according to the windows specified in Table 5 in case the premature EOT visit assessment is treatment emergent (i.e., within 30 days after study treatment discontinuation).

All efficacy assessments (including unscheduled ones) are assigned to analysis visits as follows: If a subject has two or more assessments in one visit window, the assessment closest to the target day will be used as the analysis visit for that visit window. The other additional assessment(s) will not be used in by-visit summaries or analyses, but they can be used for determination of other endpoints (e.g., time to event endpoints). If two assessments are equidistant from the target day within a visit window, the later visit is used. If more than one value falls on the same timepoint then the one with the worst assessment (i.e., lowest peak VO_2, VO_2 at VAT, PA-Ac mean count per minute) is used. All assignments will be made in chronological order. Once an assessment is assigned to a visit window, it will no longer be used for a later time point.

Assessments which fall outside of any planned window will not be included in by-visit summary tables and graphs but will be included in outlier tables and into individual subject listings.

Table 5: Time Windows for the OL Period and Day 30 FU

Parameter	Analysis Visit (label on output)	Time Interval (OL Day)*	Target Time Point (OL Day)
PA-Ac	OL Baseline	1 to 30	2-10
Efficacy parameters. Safety parameters (for EOT visit remapping only)	OL Week 26	92 to 273	183
	OL Week 52	274 to 455	365
	OL Week 78	456 to 637	547
	OL Week 104	638 to 819	729
	OL Week 130	820 to 1001	911
	OL Week 156	1002 to 1183	1093
Laboratory (aminotransferases and hemoglobin only)	Day 30 FU	≥ Analysis Set EOT + 28	Analysis Set EOT + 30

* Relative to OL Day 1 (defined in Section 5.1.2.2)

5.1.2. Definition of Baseline, Periods and Dates/Days

5.1.2.1. Baseline

The **DB baseline** is used as derived in the core DB study (i.e., not re-derived). Except where otherwise specified in the RUBATO DB CSR SAP, DB baseline is defined as the last non-missing assessment obtained before or on the day of the start of study treatment.

The **macitentan baseline** is defined as the last value assessed prior or on the macitentan treatment start date (either in the core RUBATO DB study or in the RUBATO OL extension) defined in Section 5.1.2.2.

Baseline in OLES is generally defined as the last non-missing assessment obtained prior or on the RUBATO OL treatment start date defined in Section 5.1.2.2. For PA-Ac, OLES baseline is based on assessments recorded after RUBATO OL treatment start date, details are given in Section 5.5.2.

Baseline in RUBATO pool and RUBATO DB set corresponds to DB baseline.

Baseline in TMAS set corresponds to macitentan baseline.

5.1.2.2. Treatment Start Date (Day 1) and Day Numbering in Analysis Sets

The **DB treatment start date (DB Day 1)** is used as derived in the RUBATO DB study (i.e., not re-derived).

The **OL treatment start date (OL Day 1)** is the date of first dose of macitentan treatment in the RUBATO OL study. This is the "Treatment start date" (defined as the date the first dose of study treatment intake) from the first interval, in chronological order, recorded in the "Study Drug Log" eCRF module of RUBATO OL.

The **macitentan treatment start date (macitentan Day 1),** is defined to be the date of first dose of macitentan either in the core RUBATO DB study or in the extension RUBATO OL. For subjects

from the macitentan group according to the SS in RUBATO DB, it is the DB treatment start date (as defined above), for subjects from the placebo group according to the SS in RUBATO DB it is the OL treatment start (as defined above).

OLES Day 1 corresponds to OL treatment start date (OL Day 1).

RUBATO pool Day 1 and RUBATO DB Day 1 set correspond to DB treatment start date (DB Day 1).

TMAS Day 1 corresponds to macitentan treatment start date (macitentan Day 1).

All safety and efficacy assessments/events (with the exception of Fontan-palliated clinical worsening and Fontan-palliated morbidity) at all visits will be assigned a day relative to analysis set Day 1.

Day or relative day for a visit/ assessments/event is defined as:

- Visit/assessment/event date − Date of analysis set Day 1 + 1, if visit/assessment/event date is ≥ date of analysis set Day 1
- Visit date/assessment/event − Date of analysis set Day 1, if visit/assessment/event date < date of analysis set Day 1

There is no 'Day 0'.

Day of Fontan-palliated clinical worsening and Fontan-palliated morbidity in the RUBATO pool is calculated relative to the randomization date:

- Date of Fontan-palliated clinical worsening / morbidity – Randomization Date + 1

5.1.2.3. End of Treatment (EOT) Date

DB EOT corresponds to study treatment end date as defined in the RUBATO DB CSR SAP.

OL EOT is only defined for subjects treated with OL treatment and corresponds to "Treatment end date" from the last interval, in chronological order, recorded in the "Study Drug Log" eCRF form.

Macitentan EOT is defined to be the date of last dose of macitentan either in the RUBATO DB study or in the extension RUBATO OL. For subjects from the macitentan group according to the SS RUBATO DB who did not enter the RUBATO OL study, this is the DB EOT (as defined in above), otherwise it is the OL EOT as defined above.

EOT in OLES corresponds to OL EOT.

EOT in RUBATO pool corresponds to OL EOT for subjects treated with OL treatment, and to DB EOT for subjects not treated with OL treatment.

EOT in TMAS corresponds to macitentan EOT.

5.1.2.4. End of Study (EOS) Date

DB EOS corresponds to EOS date as defined in the RUBATO DB CSR SAP.

OL EOS is only defined for subjects treated with OL treatment and corresponds to the date entered on the 'Visit Summary-EOS' eCRF Form. For subjects who died, EOS corresponds to the date of death. If a subject is lost to follow-up, EOS corresponds to the date of last successful contact from the 'Study Discontinuation' eCRF form.

EOS in OLES corresponds to OL EOS.

EOS in RUBATO pool and in TMAS corresponds to OL EOS for subjects treated with OL treatment, and to DB EOS for subjects not treated with OL treatment.

5.1.2.5. DB Period

All visits, assessments and events dated prior to the OL treatment start date (as defined in Section 5.1.2.2) are considered to belong to the DB period. For subjects not in the OLES (i.e., those not dosed with OL treatment), all data collected in RUBATO DB database is included and assigned to DB period.

5.1.2.6. OL Period

It is the period between OL treatment start date (as defined in Section 5.1.2.2) and OL EOS (as defined in Section 5.1.2.4), limits included.

5.2. Participant Dispositions

As per protocol amendment 3 (protocol version 4), RUBATO OL was planned to continue for each subject until the last subject has globally completed 104 weeks (2 years) of treatment. Subjects who enrolled the into RUBATO OL (i.e., were treated with OL treatment) and who did not consent to protocol version 4, but completed 104 weeks of OL treatment and the corresponding S-FU period under protocol version 3, are considered treatment and study completers in the OL period.

The following definitions are relevant to provide the disposition information.

5.2.1. Study Treatment Discontinuation

The number and percentage of subjects who discontinued study treatment (incl discontinuation reasons) in the analysis set are presented for the RUBATO OLES and the RUBATO TMAS.

In both studies, study treatment discontinuations are collected in the "Study Drug Log" eCRF form and identified as those with a treatment end date and associated reason ('What was the reason for treatment end?') answered 'Premature Discontinuation'. Reasons for study treatment discontinuation are collected in the "Premature Discontinuation of Study Treatment' eCRF form. The following reasons for permanent treatment discontinuation are displayed (including if documented to be "COVID-19 related" as per prefix in database):

- Death

- Lost to follow-up
- Pre-specified study treatment discontinuation criteria
- Adverse Event *(this combines reports of subject and physician decision)*
- Lack of Efficacy *(this combines reports of subject and physician decision)*
- Other
  - Other medical reasons *(this combines reports of subject and physician decision)*
  - Other non-medical reasons *(this combines reports of subject and physician decision)*
  - No reason provided (Subject decision)
  - Sponsor decision - Study termination
  - Sponsor decision - Other

For analyses based on the RUBATO TMAS an additional Study Treatment Discontinuation reason is defined as

- Completed treatment in RUBATO DB study but not enrolled into RUBATO OL study

For the RUBATO OLES, only RUBATO OL eCRF forms are considered whereas for the RUBATO TMAS, information is concatenated from both study eCRFs. For subjects who prematurely discontinued study treatment in the DB study and who entered the OL study after completing the week 52 PTOP visit in the DB study, the study treatment discontinuation reason in DB is not considered for treatment disposition in RUBATO TMAS.

An individual listing of subjects who discontinued study treatment prematurely and related reason(s) will be provided for the RUBATO OLES and the RUBATO TMAS.

5.2.2. Study Discontinuation

The number and percentage of subjects who prematurely discontinued study (including discontinuation reasons) in the analysis set is presented for the RUBATO OLES and the RUBATO TMAS.

In both studies, study treatment discontinuations are collected in the “Study Discontinuation” eCRF page.

Subjects who withdrew from the study are those with any withdrawal reason entered in the “Study Discontinuation” eCRF module. The following reasons for study discontinuation are displayed (including if documented to be “COVID-19 related” as per prefix in database):

- Death
- Lost to follow-up
- Adverse Event *(this combines reports of subject and physician decision)*

- Lack of Efficacy *(this combines reports of subject and physician decision)*
- Other
  - Other medical reasons *(this combines reports of subject and physician decision)*
  - Other non-medical reasons *(this combines reports of subject and physician decision)*
  - No reason provided (Subject decision)
  - Sponsor decision - Study termination
  - Sponsor decision - Other

For analyses based on the RUBATO TMAS an additional Study Discontinuation reason is defined as:

- Completed DB study but not enrolled into RUBATO OL study

For the RUBATO OLES, only RUBATO OL eCRF forms are considered whereas for the RUBATO TMAS, information is concatenated from both study eCRF and OL disposition overwrites DB disposition.

An individual listing of subjects who discontinued study prematurely and related reason(s) will be provided for the RUBATO OLES and the RUBATO TMAS.

5.2.3. Other Disposition Information

For the RUBATO OLES, the study and treatment disposition as defined in the RUBATO DB SAP will be presented to inform on the number of subjects seamlessly entering the RUBATO OL study versus subjects enrolling into OL after entering the DB study PTOP.

In addition, the distribution (number and percentage of subjects) by geographical region, country, and site ID will be presented for the RUBATO OLES and the RUBATO TMAS.

The number of subjects in the different analysis sets will be tabulated and a listing of subject membership in the different analysis sets is provided.

5.3. Extent of Exposure and Compliance

Exposure and compliance variables are derived and summarized for the RUBATO OLES, RUBATO pool (SS), and the RUBATO TMAS.

The exposure within an analysis set is evaluated first in terms of study treatment duration, including study treatment interruptions. The study treatment exposure (in days) in analysis set is calculated as:

$$treatment\ end\ date\ in\ analsis\ set - treatment\ start\ date\ in\ analysis\ set + 1$$

In addition, the study treatment exposure is evaluated in terms of actual days exposed to study treatment, excluding any temporary 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' or 'Temporarily interrupted not due to an AE' ("Study Drug Log" eCRF form), corresponding treatment end dates, and treatment restart dates are taken from the "Study Drug Log" eCRF form. For the RUBATO pool and the RUBATO TMAS, also gaps between DB EOT (defined in Section 5.1.2.3) and OL treatment start date (defined in Section 5.1.2.2) are considered as interruption. Treatment interruptions and gaps between DB EOT and OL treatment start of more than 30 days are flagged.

The study treatment exposure, excluding any temporary interruptions, is calculated as:

$$Study\ treatment\ exposure\ in\ analysis\ set\ - \\ total\ duration\ of\ interruptions\ in\ analysis\ set.$$

Where the total duration of interruptions is the sum of all treatment interruptions. The duration of each treatment interruption is calculated as:

$$Treatment\ restart\ date\ (or\ OL\ start\ date) - \\ treatment\ end\ date\ (or\ DB\ treatment\ end\ date) - 1.$$

Compliance is assessed as a percentage based on exposure as defined above from the study drug log, calculated for each pool as follows:

$$\frac{Study\ treatment\ exposure\ in\ analysis\ set\ excluding\ interruptions\ \times\ 100}{Study\ treatment\ exposure\ in\ analysis\ set}$$

Note: Compliance below 100% must not be indicative of a deviation from the protocol since there are protocol mandated reasons for interruptions and a protocol allowed gap in transition from DB to OL study.

Corresponding categorical variables (not mutually exclusive) are derived for compliance in the categories:

- < 80 %
- ≥ 80 %

The study treatment exposure (i.e., duration of treatment including interruptions) and study treatment exposure excluding any interruptions will be expressed in weeks for summary tables (i.e., calculated days of exposure are divided by 7), and corresponding categorical variables (not mutually exclusive) are derived (i.e., ≥24, ≥48, ≥72, ≥96, ≥120, ≥144 weeks). The number and percent of subjects with 0, 1 or >1 treatment interruptions of >30 days are presented in the exposure table.

Exposure and compliance variables are summarized for the RUBATO OLES, RUBATO pool (SS) (Maci/Maci arm only), and the RUBATO TMAS by means of descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range) for the continuous variables and by means of number and percentage of subjects for categorical variables.

Study drug log data and derived exposure and compliance data will be also listed for the RUBATO OLES and the RUBATO TMAS.

5.4. Safety Analysis

The following safety endpoints are defined for analysis:

- Treatment-emergent AEs and SAEs up to 30 days after study treatment discontinuation;
- AEs leading to death;
- AEs leading to premature discontinuation of study treatment;
- AEs of special interest (anemia/hemoglobin decrease, hepatic adverse events of special interest, hypotension, edema and fluid retention) and COVID-19 related AEs. AEs of special interest (AESI) and COVID-19 related AEs are defined using a selection of preferred terms (Internal MedDRA Query). The full definition is included in Section 6.7 Appendix 7;
- (Change in) vital signs (systolic and diastolic arterial BP and pulse rate), including peripheral oxygen saturation (SpO_2) and body weight over time;
- Treatment-emergent decrease in systolic blood pressure (SBP) up to 30 days after study treatment discontinuation;
- Treatment-emergent marked laboratory abnormalities up to 30 days after study treatment discontinuation;
- (Change in) laboratory parameters over time;
- (Change in) echocardiography parameters over time;
- Treatment-emergent echocardiography abnormalities (valvular defects) up to 30 days after study treatment discontinuation.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation [SD], median and range [minimum and maximum] and IQ range. Categorical variables will be summarized using frequency counts and percentages. Unless otherwise specified, data are summarized by the treatment arms defined in Table 3 for the corresponding analysis set.

5.4.1. Adverse Events

An adverse event (AE) is defined as any term reported by the Investigator in the "Adverse Event" eCRF form. The original terms used by the Investigators to describe AEs are assigned preferred terms (PT) and system organ class (SOC) for classification and tabulation using the latest implemented MedDRA version dictionary.

Any AE occurring at or after the study treatment start within the analysis set up to 30 days after the analysis set EOT (limits included) is considered to be treatment-emergent.

The following definitions are relevant for the analysis of the adverse events.

- Frequency of the adverse events

All AEs reported more than once within a subject (as qualified by the same preferred term(s)) 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.

- Intensity of the adverse events

For AEs reported more than once for a subject (as qualified by the same preferred term(s)) but with different intensities, the worst intensity is considered. The categories of intensity are defined as follows: mild, moderate and severe. If intensity is missing, the event is considered severe.

- Relationship of the adverse events

Relationship to study treatment is defined as 'related' (yes) or 'not related' (no). For 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. Adverse events with missing relationship are considered in any analysis as related.

- 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 'Drug withdrawn'.

- Serious adverse events

A SAE is an AE for which the corresponding 'Serious?' field in the eCRF AE form is ticked 'Yes'. If the information on seriousness is missing, the adverse event is considered serious.

- AEs with fatal outcome

An AE is considered having fatal outcome if the tick box "Fatal" for "Outcome" on the eCRF Adverse Event page is checked.

- Adverse events of special interest (AESIs) and COVID-19 related AEs

AEs of special interest are defined using a selection of preferred terms (Internal MedDRA Query) as detailed in Section 6.7 Appendix 7 Adverse Events of Special Interest and COVID-19 related AEs.

- Incidence rate per 100 subject-years of observation (SYO)

In order to account for differences in the time of observation among subjects, for some event types, tables will present the subject-years of observation (SYO) and the incidence rates per 100 subject-years. The subject-observation time will be calculated, for each subject, as follows:

1. For subjects without event of interest: by considering the treatment duration as (EOT date – treatment start date + 1);

2. For subjects with event of interest: by considering the treatment duration up to the start date of first event (min [date of first event, EOT date] – treatment start date + 1)

SYO will be calculated by first summing the subject-observation time for all subjects and then dividing the results by 365.25 days.

The incidence rate for the event of interest, per 100 subject-years, will be calculated by dividing the number of subjects with event of interest by the SYO and multiplying by 100:

Adjusted Incidence Rate = 100 × (Number of subjects with at least one event of interest / SYO)

- Pooling of AEs

For the RUBATO TMAS and RUBATO pool, AEs from DB and OL study are pooled. AEs that started in the DB study and were still ongoing on Day 1 of the OL study are reported in the 'Ongoing Adverse Events from AC-055H301' OL eCRF form. AEs included in the OL eCRF as 'ongoing' from the DB study and the original AEs included in the DB eCRF will be merged using a dedicated ID linking variable included in the related SDTM datasets. If the event worsened in intensity/seriousness after start of study treatment in the OL study, such an event was reported in the usual Adverse Event OL eCRF Form.

The following rules will be used by merging the SDTM datasets:

  - The outcome as entered in OL study will be used for the analysis (even if not yet entered due to AE still ongoing)
  - If the action taken for an ongoing AE is given as temporarily interrupted in the DB study database, and the action taken is missing, none, not applicable, or unknown in the OL study database, then the value from the DB will be retained. For all the other cases the action taken as entered in OL study will be used for the analysis

If an event with (partially) missing onset date in the DB study is also entered on the form "Ongoing adverse events from AC-055H301" eCRF page in the OL, this AE will not be considered as treatment-emergent with respect to the OL period (i.e., in subjects of the RUBATO TMAS receiving placebo during DB study), and no dates or other variables will be imputed if missing or partial. Such events will appear in listings only and flagged as DB period event.

All adverse event summary tables described below will be provided for the RUBATO OLES, the RUBATO TMAS, and for the Macitentan 10 mg/Macitentan 10 mg arm of the RUBATO pool (SS), if not otherwise specified.

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

- Treatment-emergent AE
- Treatment-emergent AE related to study treatment

- Treatment-emergent serious AE (SAE)
- Treatment-emergent SAE related to study treatment
- AEs leading to premature discontinuation of study treatment
- Treatment-emergent Fatal (leading to death) AE
- Severe treatment-emergent AE

In order to account for differences in the time of observation among subjects in the RUBATO TMAS, and for the Macitentan 10 mg/Macitentan 10 mg arm of the RUBATO pool (SS), the subject-years of observation (SYO) and the incidence rate per 100 subject-years will be presented for the following categories of AEs:

- Treatment-emergent serious AE (SAE)
- AEs leading to premature discontinuation of study treatment

Separate summary tables (containing number and percentages of subjects) will be provided by SOC and PT within each SOC for the following categories of AEs:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- AEs leading to discontinuation of study treatment
- Treatment-emergent AEs related to study treatment
- Treatment-emergent SAEs related to study treatment
- Treatment-emergent SAEs leading to discontinuation of study treatment
- Treatment-emergent Fatal AEs.

The summary tables are presented in descending order (e.g., SOC and PT within each SOC with the highest number of occurrences appears first). For the summaries on the RUBATO OLES, sorting is done considering the treatment arms in the following sequence: OL Macitentan 10 mg, DB-Macitentan 10 mg, DB-Placebo. In case of equal frequency of different SOC/PTs, alphabetical order is used.

Similarly, separate summary tables (containing number and percentages of subjects) will be provided by PT for the following categories of AEs:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- AEs leading to discontinuation of study treatment
- Treatment-emergent AEs related to study treatment
- Treatment-emergent SAEs related to study treatment

- Treatment-emergent SAEs leading to discontinuation of study treatment
- Treatment-emergent AEs by maximum intensity
- Treatment-emergent AESI, serious AESI, AESI leading to discontinuation of study treatment, AESI with fatal outcome
- Treatment-emergent COVID-19 related AEs, serious COVID-19 related AEs, COVID-19 related AEs leading to discontinuation of study treatment, COVID-19 related AEs with a fatal outcome

For each category of AESI, and for COVID-19 related AEs, an overall summary table will be provided, containing number and percentages of subjects having experienced at least 1 occurrence for the following categories: Any AE (plus worst severity of any AE), Any related AE, Any fatal AE, Any SAE, Any related SAE, Any AE leading to discontinuation of study treatment. For the incidence of subjects with any AESI/COVID-19 related AE, this table will also present 95% Clopper-Pearson CL, and the subject-years of observation (SYO) plus incidence rate per 100 subject-years.

In addition to the summary tables, listings will be provided based on the RUBATO pool (SS), displaying:

- AEs
- SAEs
- AEs leading to discontinuation of study treatment
- AEs of special interest
- All AEs in subjects who had any COVID-19 related AE
- All AEs in subjects who had at least one treatment interruption of >30 days. In this listing, AEs with onset date during the interruption(s) are flagged along with the "Day of AE onset relative to last intake prior to treatment interruption" derived as AE start date – treatment end date prior to interruption + 1. Only events with a start date during an interruption of >30 days are flagged this way.

For each AE it will be flagged if started in OL or DB period and whether considered treatment-emergent.

5.4.2. Deaths

A summary table will be provided, containing number and percentages of subjects who died on RUBATO pool (SS). Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Primary cause of death

The summary will be based on the "Death" eCRF modules from the DB and the OL eCRF. The summary table is presented by descending order of PT according to the incidence of deaths in the maci/maci treatment arm. The summary will be provided if at least 3 deaths have occurred overall. A corresponding listing is provided and for each death it will be flagged if started in OL or DB period.

5.4.3. Vital Signs

Vital signs parameters include systolic and diastolic blood pressure (mmHg), pulse rate (bpm) SpO_2 (%), and body weight (kg) and are summarized by displaying descriptive statistics for the observed values at baseline, for the observed post-baseline assessments, and for the absolute changes from analysis set baseline to each post-baseline visits/timepoint. Except for baseline, only treatment-emergent assessments will be included. Assessments dated after the study treatment start up to 30 days after analysis set EOT (limits included) are considered to be treatment-emergent.

The following nominal visits/timepoints will be displayed for the RUBATO pool (SS):

- DB Baseline ^ *(~ analysis set baseline)*
- DB Week 16
- DB Week 52
- OL Baseline ^
- OL Week 26
- OL Week 52
- OL Week 78
- OL Week 104
- OL Week 130
- OL Week 156

The following nominal visits/timepoints will be displayed for the OLES:

- OL Baseline ^ *(~ analysis set baseline)*
- OL Week 26
- OL Week 52
- OL Week 78
- OL Week 104
- OL Week 130
- OL Week 156

^ This is not a nominal visit but the derived baseline. In the RUBATO pool (SS), the same assessment may be displayed under 2 timepoints "DB Week 52" and "OL Baseline".

Data is included for analysis regardless of the location (left arm, right arm) or the position of measurement (supine or sitting).

For the RUBATO pool (SS), change from baseline in systolic and diastolic arterial BP, SpO_2 (%) and pulse rate over time will also be graphically presented based on box plots, on a time axis scaled by the target days of nominal visits at DB Week 16, DB Week 52, OL Baseline, OL Week 26, OL Week 52, OL Week 78, OL Week 104. The box indicates the interquartile range, a horizontal line within the box indicates the median, and a diamond shape indicates the mean. Whiskers denote minimum and maximum values within the boundary of +/- 1.5 times the size of the interquartile range. Circles indicate outliers from +/- 1.5 times the size of the interquartile range. A reference line at zero change is drawn.

A decrease in SBP is considered if a post-treatment SBP measurement (scheduled or unscheduled) up to 30 days after analysis set EOT (limits included) is <90 mmHg [or <85 mmHg for adolescents (<18 years old) who are < 150 cm in height] and was not present at baseline. The incidence (number, percentage, and 95% CL using ClopperPearson formula) of subjects with at least one treatment-emergent low systolic blood pressure (SBP) will be summarized for the RUBATO OLES, RUBATO pool (SS) (Maci/Maci arm only), and the RUBATO TMAS. Denominator is the number of subjects with at least one treatment-emergent SBP measurement available. For the RUBATO OLES and the RUBATO pool, the number and percentage of subjects with a decrease in SBP is also summarized by visit.

Blood pressure, pulse rate, SpO_2, height and body weight measurements will be reported in a subject listing for the RUBATO pool (SS). Position (supine or sitting) and location (left or right arm) for vital signs will be included. Each value will be flagged as assessed during OL or DB period and whether considered treatment-emergent.

5.4.4. Laboratory

Safety laboratory samples are centrally analyzed by Covance and the results are electronically transferred into the clinical databases of the two studies. In exceptional cases, the protocols allow the utilization of local laboratories. Local laboratory analysis results are entered in the eCRF. Quantitative results from local laboratories are not summarized (i.e., not included in summary statistics or graphical representations). Qualitative results like (marked) abnormality categorization, liver test elevation categories, etc. are derived from local laboratory data and summarized together with qualitative results derived from central laboratory data. Values from unscheduled visits are not included in by visit/timepoint summaries but are included in the listings and in the summaries for marked abnormalities and liver function test abnormalities.

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

Safety laboratory data are summarized by displaying descriptive statistics for the observed values at baseline, for the observed post-baseline assessments, and for the absolute changes from analysis set baseline to each post-baseline visit/timepoint. Except for baseline and FU visit, only treatment-emergent assessments will be included. Assessments dated after the study treatment start date up to and including 30 days after analysis set EOT are considered to be treatment-emergent.

The following selected parameters (SI unit) are included in the descriptive statistics summary tables:

- Hematology: Hemoglobin (g/L), Hematocrit (L/L), Leukocyte count (10^9/L), Neutrophils (10^9/L), Lymphocytes (10^9/L), Platelet count (10^9/L).
- Chemistry: Alanine Aminotransferase (U/L), Aspartate Aminotransferase (U/L), Alkaline phosphatase (U/L), Bilirubin (umol/L), Direct bilirubin (umol/L), Gamma glutamyl transpeptidase (U/L), Creatinine (umol/L), Glomerular Filtration Rate, calculated by central laboratory (mL/min/1.73m^2).
- Coagulation tests: Prothrombin Time (sec), Prothrombin Intl. Normalized Ratio (ratio).

The following visits/timepoints will be displayed for the RUBATO pool (SS):

- DB Baseline ^ *(~ analysis set baseline)*
- DB Week 16
- DB Week 52
- OL Baseline ^
- OL Week 26
- OL Week 52
- OL Week 78
- OL Week 104
- OL Week 130
- OL Week 156
- Day 30 FU (aminotransferases and hemoglobin only)

The following visits/timepoints will be displayed for the OLES:

- OL Baseline ^ *(~ analysis set baseline)*
- OL Week 26
- OL Week 52
- OL Week 78
- OL Week 104
- OL Week 130

- OL Week 156
- Day 30 FU (aminotransferases and hemoglobin only)

^ This is not a nominal visit but the derived baseline. In the RUBATO pool (SS), the same assessment may be displayed under 2 timepoints “DB Week 52” and “OL Baseline”.

Further analyses as described below will be conducted based on the RUBATO pool (SS), and for hematology parameters hemoglobin, hematocrit, leukocytes, platelets and chemistry parameters ALT, AST, Alkaline phosphatase, total bilirubin, creatinine. Only treatment emergent measurements are included:

- The change from baseline over time is presented based on box plots, on a time axis scaled by the target days of nominal visits at DB Week 16, DB Week 52, OL Week 26, OL Week 52, OL Week 78, OL Week 104. The box indicates the interquartile range, a horizontal line within the box indicates the median, and a diamond shape indicates the mean. Whiskers denote minimum and maximum values within the boundary of +/- 1.5 times the size of the interquartile range. Circles indicate outliers from +/- 1.5 times the size of the interquartile range.

All laboratory tests provided by the central and local laboratory will be listed together for the RUBATO pool (SS), including those from unscheduled visits. Marked laboratory abnormalities (MLAs) are flagged accordingly. Each value will be flagged as assessed during OL or DB period and whether considered treatment-emergent.

5.4.4.1. Marked Laboratory Abnormalities

A laboratory test abnormality is defined as any value outside the normal range as provided by the central and local laboratory. The direction of the abnormality (below or above the normal range) is indicated using ‘H’ and ‘L’.

A marked laboratory abnormality (MLA) is defined as any value that fulfills the applicable condition for LL/HH, as provided in Table 6. The marked laboratory abnormalities (MLA) are derived according to the protocol and listed in Table 6 below. More severe marked abnormalities are indicated by LLL/HHH/HHHH, where applicable.

The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events (CTCAE [CTCAE 2010]) grading system and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known pharmacodynamic effect of the study treatment (e.g., LLL threshold for lymphocytes).

All laboratory data are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments, and regardless of whether they were analyzed by local or central laboratory.

Treatment-emergent MLAs are all marked laboratory abnormalities occurring after the study treatment start in the analysis set and up to 30 days after analysis set EOT, that were not present at analysis set baseline (see Section 5.1.2.1 for definition) in the same or worse category (considering

the direction of worsening). In other words, the MLAs are evaluated separately for both directions of worsening (e.g., a post-baseline MLA of "HH" is considered treatment-emergent if the baseline is "L" or "LL" or "LLL" (where applicable) or "H", or within normal limits or missing. On the other hand, it is not considered as treatment-emergent if the baseline is "HH" or "HHH" when applicable). In case of missing baseline, an MLA is considered to not have been present at baseline.

Table 6: Thresholds for Marked Laboratory Abnormalities

Parameter (SI unit)	LL	LLL	HH	HHH
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)
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999
Eythrocyte count (10^{12} /L)	ND	ND	ND	ND
Leukocyte count (10^9 /L)	< 3.0	< 1.9	> 20.0	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.2	> 4.0	>20
Neutrophils (10^9 /L)	< 1.5	< 1.0	ND	ND
Eosinophils (10^9 /L)	ND	ND	> 5.0	ND
AST (U/L)*	ND	ND	≥ 3 ULN	≥ 5 ULN ≥ 8 ULN (included as HHHH)
ALT (U/L)*	ND	ND	≥ 3 ULN	≥ 5 ULN ≥ 8 ULN (included as HHHH)
Total bilirubin (umol/L)	ND	ND	≥ 2 ULN	≥ 5 ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 ULN	> 5 ULN
INR*	ND	ND	≥ 1.5 ULN or ≥ 1.5 × above baseline if on anticoagulation	≥ 2.5 ULN or ≥ 2.5 × above baseline if on anticoagulation
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 × above baseline (if baseline > ULN)	> 3 ULN or >3 × above baseline (if baseline > ULN)
eGFR (mL/min/1.73 m^2)	< 60	< 30	ND	ND
Blood Urea Nitrogen (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
Albumin (g/L)	< 30	< 20	ND	ND
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	>13.9
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	ND	< 130	> 150	> 155
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4
Cholesterol (mmol/L)*	ND	ND	> 7.75	> 12.92

The above values come from the protocol Table 4 of the protocol.

* HH and HHH based on CTCAE 2010 v4.03 (CTCAE 2010)
ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; INR = International Normalized Ratio; NA = not applicable; ND = not defined; SI = international system of units; ULN = upper limit of normal.
For INR, a subject is considered to be on anticoagulation if the subject took antithrombotic agent (ATC codes B01A) and date of INR assessment is on or after start of anticoagulation therapy.

For each category (i.e., LL, LLL, HH, HHH, HHHH), the number and percentage of subjects with at least one treatment-emergent MLA will be summarized (separately for hematology/coagulation tests and clinical chemistry). Denominator is the number of subjects with at least one treatment-emergent measurement of the corresponding laboratory parameter available. This summary is provided for the RUBATO OLES, RUBATO pool (SS) (Maci/Maci arm only), and the RUBATO TMAS.

5.4.4.2. Additional Liver Function Test and Hemoglobin Abnormalities

The following elevated liver test abnormalities are considered:

- ALT or AST ≥ 3 × ULN
- ALT or AST ≥ 5 × ULN
- ALT or AST ≥ 8 × ULN
- ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (at the same sample date)
- ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN (at the same sample date)
- ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (at any post-baseline time point up to 30 days after EOT)

The following hemoglobin abnormalities are considered:

- Hemoglobin < 80 g/L
- Hemoglobin ≥ 80 g/L and < 100 g/L
- Hemoglobin < 100 g/L.

The highest ALT or AST value and the lowest hemoglobin at any post-baseline time point of assessment up to 30 days after analysis set EOT (limits included) is considered for classification in the categories above.

For each abnormality category, incidence (number, percentage, and 95% CL using Clopper-Pearson formula) of subjects with at least one treatment-emergent abnormality will be summarized. Denominator is the number of subjects with at least one treatment-emergent measurement of any of the corresponding laboratory parameters available. This summary is provided for the RUBATO OLES, RUBATO pool (SS) (Maci/Maci arm only), and the RUBATO TMAS.

Using the "evaluation of drug-induced serious hepatotoxicity" (eDISH) plots, graphical representations of maximum treatment-emergent ALT (in multiples of ULN) by maximum treatment-emergent total bilirubin (in multiples of ULN) will be produced, to identify potential Hy's Law cases for each subject. The graph will be on a log10 scale for all subjects having assessments > 0.0625 × ULN for both peaks. Two reference lines will be plotted identifying the 2 × ULN for total bilirubin and 3 × ULN for ALT. The normal subjects are on the left lower quadrant, the possible Hy's Law cases appear on the right upper quadrant. The peak is defined as the maximum value from study treatment start up to 30 days after study treatment discontinuation (for the same subjects, not necessarily the peak of ALT occurs at the same time of the peak of total bilirubin). The same plot is provided for parameter AST and both plots are produced for the RUBATO OLES, RUBATO pool (SS) (Maci/Maci arm only), and the RUBATO TMAS.

All chemistry tests provided by the central and local laboratory, including those from unscheduled visits, will be listed separately for subjects with ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (at any post-baseline time point up to 30 days after EOT) for the RUBATO pool (SS). Each value will be flagged as assessed during OL or DB period and whether considered treatment-emergent.

5.4.5. Echocardiography

Numerical echocardiography parameters include single ventricle ejection fraction (%), Fontan circulation stenosis value (%), ventricular outflow to aorta doppler velocity (m/s), vena contracta diameter (mm) and regurgitant orifice (cm^2). Single ventricle ejection fraction (%) is summarized by displaying descriptive statistics for the observed values at baseline, for the observed post-baseline assessments, and for the absolute changes from analysis set baseline to each post-baseline visits/timepoint. Except for baseline, only treatment-emergent assessments will be included. Assessments dated after the study treatment start up to 30 days after analysis set EOT (limits included) are considered to be treatment-emergent.

The following nominal visits/timepoints will be displayed for the RUBATO pool (SS):

- DB Baseline ^ *(~ analysis set baseline)*
- DB Week 52
- OL Baseline ^
- OL Week 52
- OL Week 104
- OL Week 156

The following nominal visits/timepoints will be displayed for the OLES:

- OL Baseline ^ *(~ analysis set baseline)*
- OL Week 52
- OL Week 104

- OL Week 156

^ This is not a nominal visit but the derived baseline. In the RUBATO pool (SS), the same assessment may be displayed under 2 timepoints “DB Week 52” and “OL Baseline”.

The following valvular defects are assessed:

- **Severe AV valve regurgitation** is present where the vena contracta is ≥ 7 mm or the effective regurgitant orifice is ≥ 0.4 cm^2 in a post-baseline assessment up to 30 days after analysis set EOT, and not present at baseline. In the eCRF, up to two valve regurgitation values may be collected. If both are present in the eCRF, the largest will be considered for the derivation of Severe AV valve regurgitation.

- Presence of **left ventricular outflow obstruction** is confirmed by a pulsed-wave Doppler velocity > 2.5 m/s in a post-baseline assessment up to 30 days after analysis set EOT, and not present at baseline.

For each of the defects, the incidence (number, percentage, and 95% CL using ClopperPearson formula) of subjects with at least one occurrence (scheduled or unscheduled) will be summarized for the RUBATO OLES, RUBATO pool (SS) (Maci/Maci arm only), and the RUBATO TMAS. Denominator is the number of subjects with at least one corresponding treatment-emergent echocardiography measurement available. For the RUBATO OLES and the RUBATO pool, the number and percentage of subjects with valvular defects is also summarized by visit.

Echocardiographic parameters (all numerical and valvular defects) will be reported in a subject listing for the RUBATO pool (SS). Each value will be flagged as assessed during OL or DB period and whether considered treatment-emergent.

5.5. Efficacy Analysis

The following efficacy endpoints are assessed:

Cardiopulmonary exercise testing (CPET)

- The change from analysis set baseline to each scheduled time point in peak VO_2.
- The change from analysis set baseline to each scheduled time point in VO_2 at VAT.

Physical activity measure by Accelerometer (PA-Ac)

- Change from analysis set baseline to each scheduled time point in mean count per minute of daily PA-Ac.

Other endpoints

- Composite endpoint of event related to Fontan-palliated clinical worsening (time to first occurrence of clinical worsening up to analysis set EOS).

- Composite endpoint of events related to Fontan-palliated morbidity (time to first occurrence of morbidity up to analysis set EOS).

No formal hypothesis testing will be performed, as all efficacy analyses are considered exploratory and no inferential analysis is planned for the efficacy variables.

All efficacy endpoints will be analyzed descriptively.

- All assessments (including the unscheduled ones) are considered and re-assigned to the most appropriate visit according to the rules described in Section 5.1.1.
- Listings of all efficacy variable described below will be provided for the RUBATO pool (FAS).
- To investigate the effect of switching from placebo to macitentan 10 mg, some efficacy endpoints are assessed on the RUBATO pool (FAS). Subjects will be analyzed according to the treatment they were randomized to in the RUBATO DB.
- Following 52 weeks of treatment with either placebo or macitentan 10 mg in the DB study, it must be assumed that the two populations will not be similar in terms of baseline characteristics at the start of the OL study. With this limitation acknowledged, specific efficacy endpoints will be analyzed only for the OL study (i.e., on the OLES), overall and split by DB randomized treatment.

5.5.1. Cardiopulmonary Exercise Testing (CPET)

Measurements from CPET over time will be displayed at the following analysis visits (see Section 5.1.1for assignment of assessments to analysis visits, and Section 5.1.2.1 for baseline in analysis set definitions):

The following analysis visits/timepoints will be displayed for the RUBATO pool (FAS):

- DB Baseline *(~ analysis set baseline)*
- DB Week 16
- DB Week 52
- OL Baseline
- OL Week 52
- OL Week 104
- OL Week 156

The following analysis visits/timepoints will be displayed for the OLES:

- OL Baseline *(~ analysis set baseline)*
- OL Week 52
- OL Week 104

- OL Week 156

In the RUBATO pool (FAS), the same assessment may be displayed under 2 timepoints "DB Week 52" and "OL Baseline".

The following endpoints related to CPET are defined:

- Change in peak VO_2 (mL/kg/min), from analysis set baseline to each scheduled time point.
- Change in VO_2 at VAT, from analysis set baseline to each scheduled time point.

Derived as:

Value at scheduled timepoint – Value at analysis set baseline

The values used for peak VO_2 and VO_2 at VAT at baseline and at each scheduled time point above (including the unscheduled ones, within the pre-defined corresponding analysis visits, see Section 5.1.1) will be based on a blinded data evaluation by the independent central reading facility. In case an assessment has been evaluated as "invalid" by the independent central reading facility, it will be ignored.

Baseline peak VO_2 and VO_2 at VAT is not re-derived for the RUBATO pool (FAS) but taken from the RUBATO DB CSR analysis.

For the OLES, baseline peak VO_2 and VO_2 at VAT are derived in a similar manner, i.e., among all available measurements evaluated as "valid" by the central reading facility, the latest assessment prior or at the OL treatment start date (see Section 5.1.2.2) is considered baseline. If no "valid" assessment exists, baseline is imputed with the median value observed at baseline from the remaining subjects (within the DB treatment arm, i.e., DB-placebo or DB-Macitentan 10 mg).

No imputation of missing or invalid post-baseline peak VO_2 and VO_2 at VAT is performed, i.e., data summaries will be based on observed measurements (excluding invalid results).

Peak VO_2 and VO_2 at VAT will be summarized displaying descriptive statistics for the observed values at baseline, for the observed value at each post-baseline assessment, and for the absolute changes from baseline to each post-baseline assessment in analysis sets RUBATO OLES and RUBATO pool (FAS). For the RUBATO pool (FAS), to graphically display changes, a plot of the mean changes (±SE) in peak VO_2 and in in VO_2 at VAT from analysis set baseline over time will be displayed by treatment arm. A reference line is included at zero change and baseline is added to the time axis to visualize an initial change from zero.

In addition, for the RUBATO pool (FAS), Spaghetti plots will be presented by treatment arm to explore the longitudinal pattern of change from baseline in Peak VO_2 and VO_2 at VAT considering all the observed values (from scheduled or unscheduled assessments) and the actual assessment day in RUBATO pool.

Peak VO_2 and VO_2 at VAT will be reported in a subject listing for the RUBATO pool (FAS). Each value will be flagged as assessed during OL or DB period.

5.5.2. Physical Activity Measure by Accelerometer

The daily physical activity (counts/min) of the subject is assessed via accelerometer during the daytime. In RUBATO DB, data are collected for 9 consecutive daily daytime periods after Visit 1, after the week 16 visit and before the week 52 visit (which may be selected as baseline for the RUBATO OLES). In RUBATO OL, data are collected for 9 consecutive daily daytime periods after the enrollment visit at Day 1 (mapped to analysis visit "OL Baseline", if available considered baseline for the RUBATO OLES), and after the visits at weeks 26, 52, and 78 visit and before the week 104 visit.

The accelerometry central reading facility will read daily counts/min and will analyze duration of daily activity and time (minutes) which will be transferred to the Sponsor.

For all post baseline assessments during OL period, the 9-day time period is selected by taking the first (in chronological order) interval of 9 consecutive days with at least 4 complete daily time periods within the corresponding time window (i.e., the 9-day time period should not necessarily fall entirely in the corresponding time window, but it should overlap with the time window for at least 1 day). All assessments (including the unscheduled ones) will be mapped based on the Study Day in analysis set (see Section 5.1.1), irrespective of premature study treatment discontinuation before the assessment. To be considered evaluable, physical activity should have been measured for at least 4 complete daily daytime periods (out of 9 consecutive days) at a specific time point of assessment. For the RUBATO pool (FAS), the mean count per minute at analysis visits "DB Baseline", "DB Week 16", and "DB Week 52" is taken from the RUBATO DB ADaM.

To derive baseline mean count per minute of daily PA-Ac for the RUBATO OLES, the PA-Ac data from the OL visit 1 is considered. The 9-day time period is selected by taking the first (in chronological order) interval of 9 consecutive days with at least 4 complete daily time periods, at or after OL treatment start date up to 30 days after OL treatment start. To be considered evaluable, physical activity should have been measured for at least 4 complete daily daytime periods (out of 9 consecutive days) at baseline. A complete day is defined as a record of at least 7 hours of daily daytime data.

The values used for the PA-Ac at baseline and each post-baseline assessment are based on data evaluation by the accelerometry central reading facility.

Mean counts per minute of daily PA-Ac are calculated by dividing the sum of all activity counts (Y axis) collected during wear time for a complete day by the number of minutes of wear time in that day across all valid days (at least 4 days out of 9 days).

The activity counts collected during wear time is identifiable with "WearFilteredAxisYcounts" in Data Transfer Specifications (DTS); the number of minutes of wear time corresponds to the "WearMinutes " variable in DTS.

A complete day is defined as a record of at least 7 hours of daily daytime data, i.e., a complete day if "WearMinutes" >=7*60, (after excluding the periods when the device was apparently not worn [Troiano 2008]).

In summary, to compute the mean counts per minute of daily PA-Ac, it is necessary to identify all complete days; if less than 4 complete days out of 9 are identified then value is missing, otherwise, if at least 4 complete days out of 9 are identified, then the value is calculated on the complete days only.

The following endpoint related to PA-Ac are defined:

- change from analysis set baseline to each scheduled time point in mean count per minute of daily PA-Ac from analysis, derived as:
  Value at scheduled timepoint – Value at analysis set baseline

Mean count per minute of daily PA-Ac will be summarized displaying descriptive statistics for the observed values at baseline, for the observed value at each post-baseline assessment, and for the absolute changes from baseline to each post-baseline assessment in analysis sets RUBATO OLES and RUBATO pool (FAS). For the RUBATO pool (FAS), to graphically display changes, a plot of the mean changes (±SE) in mean count per minute of daily PA-Ac from analysis set baseline over time will be displayed by treatment arm. A reference line is included at zero change and baseline is added to the time axis to visualize an initial change from zero.

The following analysis visits/timepoints will be displayed for the RUBATO pool (FAS):

- DB Baseline *(~ analysis set baseline)*
- DB Week 16
- DB Week 52
- OL Baseline
- OL Week 26
- OL Week 52
- OL Week 78
- OL Week 104

The following analysis visits/timepoints will be displayed for the OLES:

- OL Baseline *(~ analysis set baseline)*
- OL Week 26
- OL Week 52
- OL Week 78
- OL Week 104

In addition, for the RUBATO pool (FAS), spaghetti plots will be presented by treatment arm to explore the longitudinal pattern of change from baseline in mean count per minute of daily PA-Ac considering all the observed values (from scheduled or unscheduled assessments) and the actual assessment day in RUBATO pool.

PA-Ac data will be reported in a subject listing for the RUBATO pool (FAS). Each value will be flagged as assessed during OL or DB period.

5.5.3. Fontan-palliated Clinical Worsening and Morbidity Events

The following clinical events endpoints are assessed based on the RUBATO pool (FAS) only:

- Composite endpoint of events related to Fontan-palliated clinical worsening and,
- Composite endpoint of events related to Fontan-palliated morbidity.

The dates of occurrence of each component of the above two clinical events endpoints are reported in the eCRF.

For each composite endpoint, a subject is considered as having an event if the investigator reports the occurrence of any of the individual component in the eCRF (data from RUBATO DB and RUBATO OL are pooled for this purpose), with an event date on or after the date of randomization. Subjects who did not experience an event will be right censored at EOS (as defined in Section 5.1.2.4).

The times to clinical events are expressed in weeks and calculated as:

- For subjects with an event: the earliest date of occurrence of any of the individual components minus date of randomization plus 1 divided by 7,
- For censored subjects: the EOS date minus date of randomization plus 1 divided by 7.

Composite endpoint of events related to Fontan-palliated clinical worsening

The components of the composite endpoint of events related to Fontan-palliated clinical worsening are the following (these are all assessed by the investigator and recorded in the eCRFs):

- Unscheduled hospitalization for Fontan-palliated morbidity event.
- Signs and symptoms of heart failure, requiring change in diuretic therapy.
- Clinical worsening leading to interventions related to the Fontan-palliated condition.
- Worsening to NYHA FC III, investigator assessed using the Specific Activity Scale.
- Signs and symptoms requiring the addition of a new class of cardiovascular medication (e.g., nitrates, alpha-blockers, or Endothelin receptor antagonists (ERAs)), or insertion of a pacemaker.
- Failing-Fontan defined as one or more of the following:
  - Enlisted on the active list for heart transplantation or effective heart transplantation,

- Reoperation (e.g., mechanical circulatory support, Fontan take down, Fontan revision / conversion, AV valve repair/replacement),
- Worsening to NYHA FC IV, investigator assessed using the Specific Activity Scale,
- Protein-losing enteropathy (PLE),
- Plastic bronchitis/chyloptysis,
- Peritoneal, pleural, mediastinal, or pericardial effusions,
- Severe hepatic impairment,
- Severe renal impairment,
- Death related to Failing-Fontan.

Clinical events are reported in "Clinical worsening events" section of the eCRF.

Composite endpoint of events related to Fontan-palliated morbidity.

The components of the composite endpoint of events related to Fontan-palliated morbidity are the following:

- Ventricular tachyarrhythmia or supraventricular tachyarrhythmia,
- Thrombotic or hemorrhagic complications (including thromboembolism and hemoptysis).

Clinical events are reported in "Other Fontan-palliated morbidity events" section of the eCRFs.

For each of the two composite endpoints listed above the time to the clinical event will be analyzed, separately, using the Kaplan-Meier (KM) product limit method, providing estimates for each treatment arm and corresponding 95% two-sided CLs at DB weeks 26 and 52, and at OL Weeks 26, 52, 78, 104, 130, 156. The CLs are constructed using Greenwood's formula (Collett 2003) for the standard error of the Kaplan-Meier estimate and are added to the plot. The number of subjects at risk, censored, and with events will be computed and displayed at each time point for each group.

Data will be summarized in tables or figures, including: number of events, number of censored observations, number of subjects at risk, and KM estimates of the survival function for time-to-event variables.

The graph of the estimated survival function of the time to first composite clinical endpoint for each treatment arm obtained from the Kaplan-Meier product-limit method will be displayed up to the time at which at least 10% of all subjects remain at risk of an event. The graphical presentation follows the recommendations from (Pocock 2002).

Individual subject's listings based on the RUBATO pool (FAS) will be provided for both composite endpoints (including details of all (i.e., not only first) individual component events) separately, indicating period (OL or DB period) at time of clinical event.

5.6. Other Analyses

5.6.1. Definition of Subgroups and subgroup analyses

Table 7: Table of Subgroups for Analyses

Subgroup	Definition
Age (as defined in Section 6.2)	• 12 - <18 years • ≥ 18 years

The following analyses are presented by age subgroups in the same way as described above for the overall group:

- Study Disposition (for OLES and TMAS)
- Treatment Disposition (for OLES and TMAS)
- Demographic Characteristics (for OLES and TMAS)
- Baseline Characteristics (for OLES and TMAS)
- Study Treatment Exposure (for RUBATO pool, OLES and TMAS)
- Liver and Hemoglobin Abnormalities (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Descriptive statistics of vital signs by visit (for RUBATO and OLES)
- Overall summary table of AEs (Any AE, related AE, SAE, related SAE, AE leading to premature discontinuation of study treatment, fatal AE, severe AE) (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Treatment-emergent AEs by SOC and PT within each SOC (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Treatment-emergent AEs by PT (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Treatment-emergent SAEs by SOC and PT within each SOC (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Treatment-emergent SAEs by PT (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- AEs leading to premature discontinuation of study treatment by SOC and PT within each SOC (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- AEs leading to premature discontinuation of study treatment PT (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Treatment-emergent AESI by PT (for RUBATO pool Maci/Maci Arm, OLES and TMAS)
- Number of subjects who died and primary cause of death (for RUBATO pool)

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: List of Abbreviations

AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
CPET	Cardiopulmonary Exercise Testing
CL	Confidence Limit
CSR	Clinical study report
DB	Double Blind
DTS	Data Transfer Specifications
eCRF	Electronic case report form
EOS	End-of-Study
EOT	End-of-Treatment
FAS	Full Analysis Set
FC	Functional class
ICH	International Council on Harmonisation
LV	Left ventricle
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
NT-pro-BNP	n-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OL	Open Label
OLES	Open-label Extension analysis set
PA-Ac	Physical Activity measured by Accelerometer
PD	Protocol deviation
PT	Preferred Term
QTL	Quality Tolerance Limit
RV	Right ventricle
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard Error

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	International system of units
SMQ	Standardised MedDRA Query
SOC	System organ class
SpO_2	Peripheral oxygen saturation
SS	Safety Analysis Set
TCPC	Total cavopulmonary connection
TMAS	Total Macitentan analysis set
ULN	Upper limit of normal
VAT	Ventilatory anaerobic threshold
VO_2	Oxygen uptake/consumption [$\dot{V}O_2$ is a flow = a ratio of Volume of Oxygen by unit of time]
WHO	World Health Organization

6.2. Appendix 2: Changes to Protocol-Planned Analyses

This study was prematurely discontinued by the sponsor. Study results will be presented in an abbreviated CSR.

While all safety data obtained will be summarized, only a subset of the protocol-specified efficacy endpoints and none of the protocol-specified pharmacoeconomic endpoints will be summarized. Due to the early termination of this long-term study, only key safety data (SAE, AEs leading to discontinuation, AESI) are presented adjusted for subject-years of observation. Subgroup analyses are limited to analyses by age-group.

6.3. Appendix 3: Demographic and Baseline Characteristics

6.3.1. Demographics

Demographic data will be presented for the RUBATO OLES and the RUBATO TMAS.

Weight, Height, Body Mass Index (BMI) will be taken/derived from the analysis set baseline.

Age and sex are collected on the RUBATO OL study Demographics page and used for the RUBATO OLES and for RUBATO TMAS subjects from the placebo arm in the RUBATO DB SS. For RUBATO TMAS subjects from the macitentan arm in the RUBATO DB SS, the RUBATO DB demographics page is used.

All other demographic variables are taken from the RUBATO DB demographics page.

Table 8 presents a list of the demographic variables that will be summarized RUBATO OLES and the RUBATO TMAS. Demographics will also be summarized by subgroups as defined in Section 5.6.1.

Table 8: Demographic Variables

Continuous Variables:	**Summary Type**
Age	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 (12– <18, 18– <30, 30–<40, 40-<65, >= 65)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Not Applicable)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown)	
Geographical region (America, Europe, Asia, Oceania)	
Region (US, Non-US)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese class I 30-<35 kg/m^2, obese class II 35-<40 kg/m^2, obese class III ≥40 kg/m^2]) [a]	

[a] Body Mass index BMI (kg/m^2) is calculated in the eCRF for RUBATO DB, for RUBATO OL, it is derived as Weight (kg) / [Height (cm) / 100]^2, rounded to one decimal as done in DB eCRF. For adolescents (boys or girls) between 12 and 18 years, BMI-for-age reference equivalent to BMI cutoffs for adults are calculated as provided in Attachment 1 of the RUBATO DB CSR SAP (EDMS-RIM-264216, 1.0).

All demographic data will be reported in subject listings on the RUBATO OLES and the RUBATO TMAS.

6.3.2. Baseline Disease Characteristics

Table 9 presents a list of baseline disease characteristics variables that will be summarized RUBATO OLES and the RUBATO TMAS.

Table 9: Baseline Disease Characteristics

Continuous Variables:	**Summary Type**
Time since Fontan palliation completion (years) **at treatment start in analysis set**	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Peak VO_2 (mL/kg/min) at baseline **at analysis set baseline**	
VO_2 at VAT at baseline **at analysis set baseline**	
Mean count per minute of daily Physical Activity at baseline **at analysis set baseline**	
NT-proBNP (pmol/L) **at analysis set baseline**	
Categorical Variables	
Congenital heart defect leading to Fontan-palliation **as recorded at DB study entry**	Frequency distribution with the number and percentage of subjects in each category.
Dominant ventricular morphology (left and right/mixed) **as recorded at DB study entry**	
Staged reconstructive surgeries performed before completion of the Fontan circulation **as recorded at DB study entry**	
Type of primary TCPC Fontan completion **as recorded at DB study entry**	
Type of secondary TCPC Fontan completion (TCPC=total cavopulmonary connection) **as recorded at DB study entry**	
Fenestration Status **as recorded at DB study entry**	
PAH specific therapies concomitant at start of study treatment **in analysis set**	
NYHA FC **at analysis set baseline**	

PAH specific therapies concomitant at start of study treatment in analysis set

- PAH specific medications concomitant at start of study treatment in analysis set (see Section 6.5.3 for definition). Pulmonary hypertension specific medications are: sildenafil, sildenafil citrate, tadalafil, vardenafil, udenafil, iloprost, beraprost, epoprostenol, treprostinil, selexipag, bosentan, ambrisentan, riociguat.

All other variables that are presented, are based on data recorded at entry into study RUBATO DB will be derived as described in the RUBATO DB CSR SAP. The remaining variables are re-derived in the same manner as described in the RUBATO DB CSR SAP, based on the analysis set baseline (as defined in Section 5.1.2.1).

All baseline disease characteristics variables will be reported in subject listings on the RUBATO OLES and the RUBATO TMAS.

6.4. Appendix 4: Protocol Deviations and Quality Tolerance Limits (QTL)

The description of each protocol deviation (PD) is agreed in the sponsor protocol deviation code list (PD list Version 3, dated 20-Apr-2021). According to this document, each PD is classified as important or not important. A further categorization into one of the following categories is documented in Table 10: Entered but did not satisfy criteria, Developed withdrawal/interruption criteria but not withdrawn/interrupted, Received a disallowed concomitant treatment, Received wrong treatment or incorrect dose, Other.

Only important (i.e., major) protocol deviations will be summarized by category, displaying counts and percentages of subjects with at least one PD within each category for the RUBATO OLES. A separate similar summary of important PDs will be provided by geographical region and site. These summaries are provided for all important (i.e., major) PDs and separately for all COVID-19 related important (i.e., major) PDs.

All reported PDs and all reported COVID-19 related PDs will be reported in subject listings. Both listings are provided for the RUBATO OLES, with important PDs flagged accordingly.

Table 10: PD Classification Based on AC-055H302 (RUBATO OL)

Condition	Identifier	Important	Categorization of PD for reporting
Subject not enrolled but received study drug	PD_MM.101	Yes	Received wrong treatment or incorrect dose
Informed consent not personally signed and dated by subject /legal representative	PD_MM.102	Yes	Other
Study assessments were performed but no informed consent was signed and dated by subject/legal representative.	PD_MM.103	Yes	Other
Informed consent process (including re-consenting) not followed	PD_MM.104	Yes	Other
Subject enrolled but did not complete Week 52 of RUBATO DB	PD_MM.132	Yes	Entered but did not satisfy criteria
Woman of childbearing potential who did not have a negative serum pregnancy test prior to first intake of OL study drug	PD_MM.133	Yes	Entered but did not satisfy criteria
Other violation before enrollment not listed above	PD_MM.105	No	Other
Woman of childbearing potential who did not agree to perform monthly pregnancy tests up to the end of the S-FU period	PD_MM.134	Yes	Entered but did not satisfy criteria
Woman of childbearing potential who did not agree to use reliable contraception from enrollment and up to at least 30 days after study drug discontinuation	PD_MM.135	Yes	Entered but did not satisfy criteria
Clinical worsening leading to medical interventions including reoperation of Fontan circulation during the enrollment period	PD_MM.136	Yes	Entered but did not satisfy criteria
Systolic BP < 90 mmHg (< 85 mmHg for subjects < 18 years old and < 150 cm of height) at rest	PD_PM.325	Yes	Entered but did not satisfy criteria
Hemoglobin < 75% of the lower limit of normal assessed by central laboratory at enrollment	PD_PM.326	Yes	Entered but did not satisfy criteria
Known or suspected pulmonary veno-occlusive disease	PD_MM.137	Yes	Entered but did not satisfy criteria
Known and documented severe hepatic impairment defined as Child-Pugh Score C	PD_MM.138	Yes	Entered but did not satisfy criteria
Serum AST and/or ALT > 3 x upper limit of normal range assessed by central laboratory at enrollment	PD_PM.327	Yes	Entered but did not satisfy criteria
Severe renal impairment (estimated creatinine clearance < 30 mL/min/1.73m2) assessed by central laboratory at enrollment	PD_PM.328	Yes	Entered but did not satisfy criteria

Condition	Identifier	Important	Categorization of PD for reporting
Hypersensitivity to any active substance or excipient of any of the study drugs	PD_MM.139	Yes	Entered but did not satisfy criteria
Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer within 1 month prior to enrollment (Visit 1)	PD_MM.140	Yes	Entered but did not satisfy criteria
Treatment with a strong CYP3A4 inhibitor within 1 month prior to enrollment (Visit 1)	PD_MM.141	Yes	Entered but did not satisfy criteria
Treatment with a moderate dual CYP3A4/CYP2C9 inhibitor (e.g., fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors within 1 month prior to enrollment (Visit 1)	PD_MM.142	Yes	Entered but did not satisfy criteria
Any factor or condition likely to affect protocol compliance of the subject, as judged by the investigator	PD_MM.143	Yes	Entered but did not satisfy criteria
Treatment with another investigational therapy during the OL study	PD_MM.144	Yes	Entered but did not satisfy criteria
Treatment with ERAs other than macitentan	PD_MM.145	Yes	Entered but did not satisfy criteria
Known drug or substance (e.g., alcohol) abuse, unstable psychiatric illness, or any other condition that, in the opinion of the investigator, may interfere with participation in the study	PD_MM.146	Yes	Entered but did not satisfy criteria
Any planned surgical intervention (e.g., organ transplant) during the study period, except minor interventions (e.g., tooth extraction)	PD_MM.147	Yes	Entered but did not satisfy criteria
Any known factor or disease that may interfere with treatment compliance or full participation in the study (e.g., chemotherapy treatment for cancer) or illness with an anticipated life expectancy of less than 12 months.	PD_MM.148	Yes	Entered but did not satisfy criteria
PA-Ac device not correctly assigned or initiated at enrollment	PD_MM.149	Yes	Other
Subject not contacted to remind them to wear PA-Ac device	PD_MM.150	No	Other
Enrollment assessment not done/missing	PD_PP.202	Yes	Other
Pregnancy testing at enrollment not done	PD_PM.301	Yes	Other
Entry enrollment labs are > 4 weeks after EOT Visit in AC-055H301 RUBATO DB	PD_PM.302	Yes	Other
Study drug not withheld prior to assessments at enrollment visit	PD_MM.106	No	Other
CPET at Visit 1 conducted under different conditions than during the AC-055H301 RUBATO DB study	PD_MM.107	No	Other
CPET at Visit 1 done, but not valid/questionable on review by central reading facility	PD_MM.108	No	Other
CPET at Visit 1 not done according to guidelines and central reader manual	PD_MM.109	No	Other
CPET at Visit 1 not done (but required)	PD_MM.151	No	Other
SAE not reported within 24 hours of knowledge, or not reported as per protocol	PD_MM.110	Yes	Other
Other violation at enrollment not listed above	PD_MM.111	No	Other
Subject has no post-baseline safety assessment	PD_PM.303	Yes	Other
Subject has no post-baseline efficacy assessment	PD_PM.304	Yes	Other
PA-AC device not returned/device lost/issues with upload	PD_MM.152	No	Other

Condition	Identifier	Important	Categorization of PD for reporting
Subject does not have sufficient PA-Ac baseline data	PD_PM.305	No	Other
Visit 2 assessment not done/missing	PD_PP.203	Yes	Other
Visit 2 vital signs assessed under different conditions than at baseline	PD_MM.116	No	Other
Visit 2 labs missing/incomplete	PD_PM.306	Yes	Other
Study drug not withheld prior to assessments at Visit 2	PD_MM.117	No	Other
PA-Ac device not correctly assigned or initiated at Visit 2	PD_MM.153	No	Other
Subject does not have sufficient PA-Ac data at Visit 2	PD_PM.329	No	Other
Subject not contacted to remind them to wear PA-Ac device	PD_MM.154	No	Other
PA-Ac device not returned/lost device/upload problems	PD_MM.155	No	Other
CPET at Visit 3 conducted under different conditions than at baseline	PD_PM.307	No	Other
CPET at Visit 3 done, but not valid/questionable on review by central reading facility	PD_PM.308	No	Other
CPET at Visit 3 not done according to guidelines and central reader manual	PD_MM.118	No	Other
CPET at Visit 3 not done	PD_PP.204	No	Other
Visit 3 assessment not done/missing	PD_PP.205	Yes	Other
Visit 3 vital signs assessed under different conditions than at baseline	PD_MM.119	No	Other
Subject does not have sufficient PA-Ac data at Visit 3	PD_PM.309	No	Other
Visit 3 labs missing/incomplete	PD_PM.310	Yes	Other
Study drug not withheld prior to assessments at Visit 3	PD_MM.120	No	Other
Visit 4 assessment not done/missing	PD_PP.206	Yes	Other
Visit 4 vital signs assessed under different conditions than at baseline	PD_MM.121	No	Other
Subject does not have sufficient PA-Ac data at Visit 4	PD_PM.311	No	Other
Visit 4 labs missing/incomplete	PD_PM.312	Yes	Other
Study drug not withheld prior to assessments at Visit 4	PD_MM.122	No	Other
Visit 5 assessment not done/missing	PD_PP.207	Yes	Other
CPET at Visit 5 conducted under different conditions than at baseline	PD_PM.313	No	Other
CPET at Visit 5 done, but not valid/questionable on review by central reading facility	PD_MM.123	No	Other
CPET at Visit 5 not done according to guidelines and central reader manual	PD_MM.124	No	Other
CPET at Visit 5 not done	PD_PP.208	No	Other
Visit 5 vital signs assessed under different conditions than at baseline	PD_MM.125	No	Other

Condition	Identifier	Important	Categorization of PD for reporting
Subject does not have sufficient PA-Ac data at Visit 5	PD_PM.314	No	Other
Visit 5 labs missing/incomplete	PD_PM.315	Yes	Other
Study drug not withheld prior to assessments at Visit 5	PD_MM.126	No	Other
Visit 6 assessment not done/missing	PD_PP.214	Yes	Other
Visit 6 vital signs assessed under different conditions than at baseline	PD_MM.171	No	Other
Visit 6 labs missing/incomplete	PD_PM.332	Yes	Other
Study drug not withheld prior to assessments at Visit 6	PD_MM.172	No	Other
Visit 7 assessment not done/missing	PD_PP.215	Yes	Other
CPET at Visit 7 conducted under different conditions than at baseline	PD_PM.333	No	Other
CPET at Visit 7 done, but not valid/questionable on review by central reading facility	PD_MM.173	No	Other
CPET at Visit 7 not done according to guidelines and central reader manual	PD_MM.174	No	Other
CPET at Visit 7 not done	PD_PP.216	No	Other
Visit 7 vital signs assessed under different conditions than at baseline	PD_MM.175	No	Other
Visit 7 labs missing/incomplete	PD_PM.334	Yes	Other
Study drug not withheld prior to assessments at Visit 7	PD_MM.176	No	Other
Visit 8 assessment not done/missing	PD_PP.217	Yes	Other
Visit 8 vital signs assessed under different conditions than at baseline	PD_MM.177	No	Other
Visit 8 labs missing/incomplete	PD_PM.335	Yes	Other
Study drug not withheld prior to assessments at Visit 8	PD_MM.178	No	Other
Visit 9 assessment not done/missing	PD_PP.218	Yes	Other
CPET at Visit 9 conducted under different conditions than at baseline	PD_PM.336	No	Other
CPET at Visit 9 done, but not valid/questionable on review by central reading facility	PD_MM.179	No	Other
CPET at Visit 9 not done according to guidelines and central reader manual	PD_MM.180	No	Other
CPET at Visit 9 not done	PD_PP.219	No	Other
Visit 9 vital signs assessed under different conditions than at baseline	PD_MM.181	No	Other
Visit 9 labs missing/incomplete	PD_PM.337	Yes	Other
Study drug not withheld prior to assessments at Visit 9	PD_MM.182	No	Other
Initiation of forbidden medication	PD_PM.338	Yes	Received a disallowed concomitant treatment
Aminotransferase elevation ≥ 3 x ULN and study drug not interrupted or discontinued	PD_PM.316	Yes	Developed withdrawal/interruption

Condition	Identifier	Important	Categorization of PD for reporting
			criteria but not withdrawn/interrupted
Aminotransferase elevation ≥ 3 x ULN and retests not done per protocol	PD_PM.317	Yes	Other
Hemoglobin < 100 g/L with a decrease from baseline of ≥ 50 g/L and retest not done per protocol	PD_PM.318	Yes	Other
Hemoglobin < 80 g/L with no underlying blood loss and study treatment not interrupted	PD_PM.319	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Re-introduction of treatment before a) Aminotransferases returned to pre-treatment or normal range b) Hemoglobin returned to pre-treatment or normal range	PD_PM.320	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Blood pressure dropped < 90 mm Hg (< 85 mm Hg for subjects < 18 years old and < 150 cm of height and study drug not interrupted	PD_PM.321	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Subject got pregnant during the treatment period or within 30 days after treatment discontinuation	PD_PM.322	Yes	Other
Subject got pregnant and study drug was not interrupted	PD_PM.330	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Woman of childbearing potential not using reliable contraception	PD_PM.323	Yes	Other
Pregnancy test was missed	PD_MM.156	Yes	Other
CPET performed out of window of last QA (> 213 days since last QA)	PD_MM.127	No	Other
ECHOC not performed according to guidelines	PD_MM.128	No	Other
Subject received treatment which was not approved for use	PD_MM.157	Yes	Other
Study treatment compliance between 2 visits < 80% or > 120%	PD_PM.324	Yes	Received wrong treatment or incorrect dose
Overall study treatment compliance for the whole treatment period < 80% or > 120%	PD_MM.158	Yes	Received wrong treatment or incorrect dose
Study treatment compliance based on subject's report	PD_MM.183	No	Received wrong treatment or incorrect dose
Study medication not stored correctly but subject continued to use it	PD_MM.129	Yes	Received wrong treatment or incorrect dose
Study treatment not administered as per protocol (any dose of study treatment higher than the planned total daily dose in a single day will be considered an overdose)	PD_MM.159	Yes	Received wrong treatment or incorrect dose
Subject treatment not discontinued although subject (legally acceptable representative) decided not to continue treatment	PD_MM.160	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Subject medication not discontinued although investigator considers that the subject should not continue treatment	PD_MM.161	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Sponsor decision to withdraw subject or terminate study and subject was not discontinued within the time indicated by the sponsor	PD_MM.162	Yes	Developed withdrawal/interruption criteria but not withdrawn/interrupted

Condition	Identifier	Important	Categorization of PD for reporting
Visit 2 performed out of window (Day 183 ± 7 days)	PD_PP.209	No	Other
Visit 3 performed out of window (Day 365 ± 7 days)	PD_PP.210	No	Other
Visit 4 performed out of window (Day 547 ± 7 days)	PD_PP.211	No	Other
Visit 5 performed out of window (Day 729 ± 7 days)	PD_PP.212	No	Other
Visit 6 performed out of window (Day 911 ± 7 days)	PD_PP.220	No	Other
Visit 7 performed out of window (Day 1093 ± 7 days)	PD_PP.221	No	Other
Visit 8 performed out of window (Day 1275 ± 7 days)	PD_PP.222	No	Other
Visit 9 performed out of window (Day 1457 ± 7 days)	PD_PP.223	No	Other
Visit EOS performed out of window (EOS + 30-35 days)	PD_PP.213	No	Other
6-monthly visit performed out of window	PD_MM.163	No	Other
FU-visit performed out of window	PD_MM.164	No	Other
Visit was performed remotely/partly remotely	PD_MM.165	No	Other
SAE not reported within 24 hours of knowledge, or not reported as per protocol	PD_MM.130	Yes	Other
CPET data not sent to central reading facility within 5 working days	PD_MM.166	No	Other
Monthly lab performed out of window	PD_PM.331	No	Other
Monthly lab sample missing	PD_MM.167	Yes	Other
Consecutive lab samples missing/not available without replacement/local labs being done	PD_MM.168	Yes	Other
Oversampling during lab assessments	PD_MM.169	Yes	Other
Lab report not signed within 5 days of receipt	PD_MM.170	No	Other
Other violation during treatment period and follow-up not listed above	PD_MM.131	No	Other

During the course of this long-term safety study, two quality tolerance criteria were defined as shown in table 11 below. Both are related to participants' safety.

Table 11: Quality Tolerance Limits as per Integrated Analytical Risk-Based Monitoring Plan

Critical to Quality Factor	Parameter	Primary Threshold	Captured in PD/PD category
Subjects who meet at least one of the study specific discontinuation criteria must be permanently discontinued.	% subjects not discontinued according to protocol safety criteria.	10% subjects not discontinued according to protocol safety criteria. Special attention in the first 6 months of treatment (because of placebo roll over patients)	Developed withdrawal/interruption criteria but not withdrawn/interrupted
Safety laboratory must be done per time and events schedule in the protocol.	% of subjects with 2 missing consecutive safety lab tests and % of missing safety lab test.	10 % of subjects with 2 missing consecutive safety lab tests	PD_MM.168

6.5. Appendix 5: Prior and Concomitant Medications

All therapies as collected in the "Previous/Concomitant Medication" eCRF form of the two studies RUBATO DB and RUBATO OL will be pooled for the RUBATO OLES and the RUBATO TMAS.

The original terms used by the investigators to describe therapies are assigned preferred terms for classification and tabulation using the latest version of the World Health Organization (WHO) Drug code and Anatomic Therapeutic Chemical (ATC) class code dictionaries.

6.5.1. Prior Medications

Prior medications are defined as any therapy with an end date prior to the date of first intake of study medication in the analysis set.

If the end date is missing and the start date is prior to the date of first intake of study medication in the analysis set, and

- the checkbox for the question 'Ongoing at start of treatment?' is ticked 'No' on the RUBATO DB eCRF form, then the therapy is considered as previous for all subjects in the RUBATO OLES and the RUBATO TMAS.
- the checkbox for the question 'Ongoing at start of treatment?' is ticked 'No' on the RUBATO OL eCRF form, then the therapy is considered as previous in the RUBATO OLES for all subjects and in the RUBATO TMAS for subjects from the placebo arm in the RUBATO DB (SS). In the RUBATO TMAS it is considered concomitant for subjects from the macitentan arm in the RUBATO DB (SS) unless the same record (i.e., same therapy, same start date, missing end date, 'Ongoing at start of treatment?' ticked 'No') is also documented in the DB eCRF. In this case it is also considered previous for the RUBATO TMAS.

6.5.2. Concomitant Medications

Concomitant medications are all therapies that are ongoing at, and/or initiated before date of first intake of study medication in the analysis set and terminated after the date of first intake of study medication in the analysis set, or initiated on or after the date of first intake of study medication in the analysis set up to the date of EOT in the analysis set.

Number and percentages of subjects having taken at least one medication will be presented by Anatomic Therapeutic Chemical (ATC) class (level 4) and PT within each ATC class for the RUBATO OLES and the RUBATO TMAS. All summaries will be tabulated by ATC class, and individual preferred terms within each ATC class. ATC classes will be sorted by descending order. For the summaries on the RUBATO OLES, sorting is done considering the arms in the following sequence: OL Macitentan 10 mg, DB-Macitentan 10 mg, DB-Placebo. If the frequencies of ATC class are the same, alphabetical order will be used. The same rule applies for preferred terms within ATC class.

Subjects who took the same medication more than once (as qualified by the same PT(s)) are counted only once. In case the reported medication is assigned to several PTs, subjects are counted for each individual PT.

All medications will be reported in a subject listing including all subjects with flags to identify prior and concomitant medications accordingly, on the RUBATO OLES and the RUBATO TMAS. This listing is repeated in the subset of subjects who had any COVID-19 related AE.

6.5.3. Concomitant Medications at Start of Study Treatment in Analysis Set

Concomitant therapies at start of treatment in analysis set is any treatment that is either ongoing at the start of study treatment or is initiated at the start date of study treatment, identified as follows:

- 'Ongoing at start of treatment? = **Yes**' ticked by the investigator in the eCRF*,

  or

- Start date before or on analysis set treatment start date and end date on or after treatment start date,

  or

- Start date before or on analysis set treatment start date and end date missing with 'Ongoing at start of treatment?' ≠ **No**' in the eCRF*.

  * Based on the RUBATO OL "Previous/Concomitant Medication" eCRF form for OLES and for RUBATO TMAS subjects from the placebo arm in the RUBATO DB SS. Based on the RUBATO DB "Previous/Concomitant Medication" eCRF form for RUBATO TMAS subjects from the macitentan arm in the RUBATO DB SS.

6.6. Appendix 6: Intervention Compliance

Not applicable. Only percentage of days with study treatment exposure (excluding interruptions) of the duration of exposure (including interruptions) are reported as described in Section 5.3.

6.7. Appendix 7: Adverse Events of Special Interest and COVID-19 related AEs

Adverse events of special interest are defined as follows:

I. Hepatic events of special interest

AEs are included in this grouping if their coded PTs are included in the "Hepatic disorders" SMQ with including all its sub-SMQ with the exception of "Liver-related coagulation and bleeding disturbances (SMQ)".

II. Edema and fluid retention

AEs are included in this subgroup if their coded PTs is "Pulmonary congestion" or if within the SMQ "Haemodynamic oedema, effusions and fluid overload (SMQ)" with the exception of PTs containing "site".

III. Anemia / hemoglobin decrease

AEs are included in this grouping if their coded PTs are included in 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".

IV. Hypotension

AEs are included in this grouping if their coded PTs are: 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, Procedural hypotension, Dialysis hypotension, Hypotensive crisis, Post procedural hypotension.

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 immunisation, 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.

7. REFERENCES

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