Janssen Research & Development

Statistical Analysis Plan for iCSR

A multicenter, open-label, single-arm Phase III study to assess the efficacy, safety and pharmacokinetics of macitentan in Japanese pediatric patients (3 months to <15 years) with pulmonary arterial hypertension

Protocol 67896062PAH3001; Phase 3

JNJ-67896062/ACT-064922 (macitentan)

Status:	Approved
Date:	2 August 2023
Prepared by:	Actelion Pharmaceuticals Ltd., a Janssen Pharmaceutical Company of Johnson & Johnson
Document No.:	EDMS-RIM-1097077, 2.0

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

TABLE OF CONTENTS

VERSION HISTORY

Table 1: **SAP Version History Summary**

SAP Version	Approval Date	Change	Rationale
1.0	25 July 2023	Not Applicable	Initial release
2.0	2 August 2023	Section 5.6.4 (ECG abnormalities) and section 5.4.5 (BSA definition)	Clinical ECG abnormalities are clarified and BSA definition in section 5.4.5 is aligned with the definition in section 5.4.1

1. INTRODUCTION

The purpose of this SAP is to describe the statistical analysis and presentation of study results for the Interim Clinical Study Report (iCSR) of study 67896062PAH3001 for a CHMP line extension submission. The iCSR analyses will take place when 24 weeks data of the two first patients below 2 years of age are available, database lock planned on 09AUG2023. The analyses for the final CSR are described in a separate SAP.

Study Data Tabulation Model (SDTM) datasets will be provided and are considered the source data, but reference will also be made to the eCRF information. When appropriate, analysis data sets will be derived as SAS® data sets according to the CDISC Analysis Data Model.

Each subject will have an individual cut-off date corresponding to subject Week 24 Visit/Collection date).

1.1. Study Documents

For the preparation of this SAP the following documents are used:

- Protocol 67896062PAH3001, approved version 5, dated 09 March 2023, EDMS-RIM-454995, 5.0;
- eCRF 67896062PAH3001, version 6, dated 09MAY2023.

1.2. Objectives and Endpoint

Table 2: Objectives and Endpoints

Objectives	Endpoints*
Primary	
To evaluate the effect of Macitentan on hemodynamic measures at Week 24	Fold change at Week 24 in pulmonary vascular resistance index (PVRI)
Secondary	
To evaluate the effect of Macitentan on pulmonary hemodynamic parameters other than PVRI at Week 24	Change from baseline to Week 24 in the following hemodynamic variables: pulmonary vascular resistance (PVR), mean right atrial pressure (mRAP), mean pulmonary arterial pressure (mPAP), cardiac index (CI), cardiac output (CO), total pulmonary resistance (TPR) and mixed venous oxygen saturation (SvO_2) at rest
To evaluate the effect of Macitentan on World Health Organization (WHO) Functional Class (FC) at Week 24 (For patients whose age is >4 years of age when initial informed consent)	Improvement in WHO FC from baseline to Week 24 (yes/no).
To evaluate the effect of Macitentan on Panama FC at Week 24	Improvement in Panama FC from baseline to Week 24 (yes/no).
To evaluate the effect of Macitentan on exercise capacity at Week 24 (For patients who are developmentally able to understand and perform the 6-minute walk test [6MWT] and whose age is ≥6 years of age when initial informed consent)	Change from baseline to Week 24 in exercise capacity (6-minute walk distance [6MWD], as measured by the 6MWT).
To evaluate the effect of Macitentan on NT-proBNP at Week 24	Change from baseline to Week 24 in NT-proBNP

Objectives	**Endpoints***
To evaluate the effect of Macitentan on Echocardiography at Week 24	Change from baseline to Weeks 24 in tricuspid annular plane systolic excursion (TAPSE) and left ventricular eccentricity index measured by echocardiography.
To evaluate the effect of Macitentan on quality of life at Week 24(For patients whose age is ≥2 years of age when initial informed consent)	Change from baseline to Week 24 in: PedsQL™ 4.0 Generic Core Scales Short Form (SF15).
To evaluate the effect of Macitentan on physical activity at Week 24 (For patients whose age is ≥2 years of age when initial informed consent)	Change from baseline to Week 24 in physical activity as measured by accelerometry
To assess pharmacokinetics (PK) of Macitentan and its active metabolite (aprocitentan) in pediatric participants with PAH.	Macitentan and aprocitentan concentrations in plasma or blood at all assessed timepoints
To evaluate the long-term effect of Macitentan on exercise capacity in PAH children (For patients who are developmentally able to understand and perform 6MWT and whose age is ≥6 years of age when initial informed consent)	Changes from baseline to all assessed timepoints in exercise capacity (6MWD, as measured by the 6MWT).
To evaluate the long-term effect of Macitentan on dyspnea and exertion (For patients who perform 6MWT)	Change from baseline to all assessed timepoints in dyspnea on exertion assessed by the Borg CR10 Scale®
To evaluate the effect of Macitentan on physical activity (For patients whose age is ≥2 years of age when initial informed consent)	Change from baseline to all assessed timepoints in physical activity as measured by accelerometry
To evaluate the long-term effect of Macitentan on WHO FC (For patients whose age is >4 years of age when initial informed consent)	Improvement in WHO FC from baseline to all assessed timepoints
To evaluate the long-term effect of Macitentan on Panama FC	Improvement in Panama FC from baseline to all assessed timepoints
To evaluate the long-term effect of Macitentan on NT-proBNP	Percent of Baseline plasma NT-proBNP at each timepoint of assessment.
To evaluate the long-term effect of Macitentan on Echocardiography	Percent of Baseline in TAPSE, and left ventricular eccentricity index measured by echocardiography to all assessed timepoints
To evaluate the effect of Macitentan on quality of life (For patients whose age is ≥2 years of age when initial informed consent)	Change from baseline to all assessed timepoints in: PedsQL™ 4.0 Generic Core Scales Short Form (SF15).
To evaluate the safety and tolerability of Macitentan in pediatric participants with PAH.	Safety endpoints are assessed up to 30 days after study intervention discontinuation • Adverse events (AEs) • Serious adverse events (SAEs) • AEs leading to premature discontinuation of Macitentan • AEs of special interest • Markedly laboratory abnormalities • Change from baseline in laboratory parameters to all timepoints of assessments • Change from baseline in vital signs (diastolic blood pressure [DBP], systolic blood pressure [SBP], and pulse rate [PR]), height and body weight to all timepoints of assessments • Change from baseline in electrocardiogram (ECG) parameters

Objectives	Endpoints*
Exploratory	
To confirm the time to occurrence of the morbidity/mortality event.	Time to occurrence of any of the following events from the start of Treatment phase as defined below: • Death (all causes) • Atrial septostomy or Potts' anastomosis, or registration on lung transplant list • Hospitalization due to worsening PAH§ • Clinical worsening* of PAH defined as: Need for, or initiation of new PAH-specific therapy# or IV diuretics or continuous oxygen use AND at least one of the following: – Worsening in WHO FC, or – New occurrence or worsening of syncope (in frequency or severity as per medical judgment), or – New occurrence or worsening of at least two PAH symptoms (ie, shortness of breath/dyspnea, chest pain, cyanosis, dizziness/ near syncope, or fatigue), or – New occurrence or worsening of signs of right heart failure not responding to oral diuretics § Excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (eg, pneumonia). * Worsening from baseline. # Eg, ERA, phosphodiesterase type 5 (PDE-5) inhibitor, prostanoids, prostacyclin receptor (IP receptor) agonist, soluble guanylate cyclase stimulator
To evaluate the effect of Macitentan on PAH-related deaths and hospitalizations	Time to hospitalization or death due to PAH occurring between the first administration of study intervention and end of study (EOS).
To evaluate the effect of Macitentan on PAH-related hospitalizations	Time to hospitalization due to PAH occurring between the first administration of study intervention and EOS.
To evaluate the effect of Macitentan on PAH-related deaths	Time to death due to PAH occurring between the first administration of study intervention and EOS.
To evaluate the effect of Macitentan on death (of all causes)	Time to death (all causes) occurring between the first administration of study intervention and Study Closure.

* Throughout the document, baseline is defined as the last observed value before the first study intervention intake.

1.3. Study Design

This is a multi-center, open-label, single-arm, Phase 3 study in Japanese pediatric participants (aged between 3 months and 14 years, inclusive) with PAH, to evaluate the efficacy, safety, and PK of Macitentan. Patients with idiopathic PAH or hereditary PAH as well as PAH associated with congenital heart disease (CHD), drug or toxin induced PAH, or connective tissue disorder (CTD) and PAH associated with human immunodeficiency virus (HIV) will be enrolled if they are of WHO FC I, II, III, or IV. Eligible patients are PAH specific treatment-naïve or already treated with PDE-5 inhibitor.

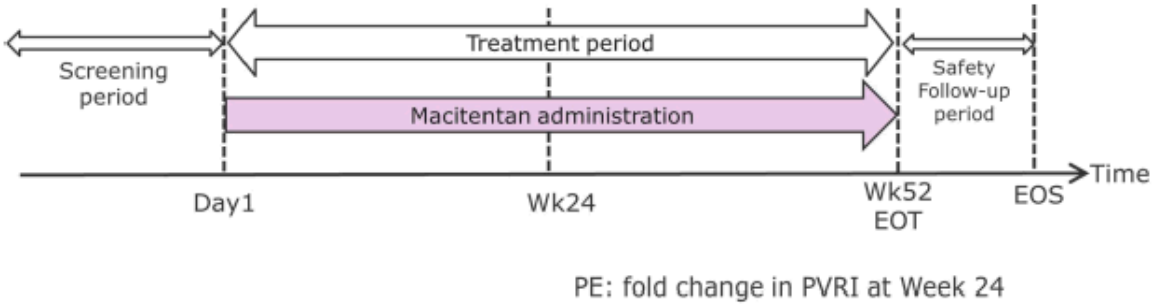
A target of 6 participants will be enrolled in this study.

The study will consist of a screening period of 30 days (Day -30 to Day -1, beginning with the signing of the informed consent/assent form [ICF]), a treatment period until Week 52 (from Day 1), and a post-treatment follow-up period (end-of-study) of 30 days after end-of treatment.

The end-of-study is considered as the last visit/assessment for the last participant in the study.

An Independent Liver Safety Data Review Board (ILSDRB) will review serious hepatic events of special interest.

Figure 1: Schematic Overview of the Study



Abbreviations: EOS=end of study; EOT=end of treatment; PE=primary endpoint; PVRI=pulmonary vascular resistance index; Wk=week.

2. STATISTICAL HYPOTHESES

There is no statistical hypothesis tested in this interventional and explorative clinical study.

3. SAMPLE SIZE DETERMINATION

A total of 6 patients will be enrolled. Details on sample size determination are described in the protocol.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For purposes of the analysis supporting a CHMP line extension submission, analysis sets are defined in Table 3.

Table 3: Analysis Sets

Analysis Sets	Description
Screened Set (SCR)	All participants who are screened and have a subject identification number
Efficacy Analysis Set	All participants enrolled.
Safety Analysis Set (SS)	All participants who take at least 1 dose of study intervention
Pharmacokinetic Analysis Set (PK)	All participants who received at least 1 administration of Macitentan and whose measured plasma or blood concentration after Macitentan administration for pharmacokinetic analysis is available.

Reasons for exclusion from Analysis Sets are listed.

5. STATISTICAL ANALYSES

5.1. General Considerations

For this iCSR, only listings will be provided.

5.1.1. Visit Windows

Not applicable

5.1.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the enrollment date. All efficacy and safety assessments at all visits are assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - date of Day 1, if visit date < date of Day 1.

There is no 'Day 0'.

5.1.3. Baseline

Baseline is the measurement obtained prior to the first administration of macitentan. If multiple measurements are available prior to the first administration of macitentan, the measurement closest to the date of the first administration will be considered as the baseline measurement.

5.1.4. Macitentan Start Date

Macitentan start date is the date of first intake of macitentan, it is the first date (in chronological order) of macitentan intake (from the study drug administration log).

5.1.5. Macitentan End Date (EOT)

Macitentan end date is the date of last intake of macitentan, it is the last date (in chronological order) of macitentan intake or the cut-off date, whichever comes first.

5.1.6. Macitentan Treatment Period

Macitentan treatment period is the period from the start to the end of macitentan administration (limits included). Possible interruptions in the drug intake are considered as part of the treatment period.

5.1.7. End of Study Date (EOS)

The EOS is considered as the last scheduled study assessment for the participant in the study.

It is defined as the date on the 'Trial Disposition (Completion/ Discontinuation)' eCRF form.

5.1.8. Imputation Rule for Missing or Incomplete Dates

Not applicable

5.2. Participant Disposition

Listings of participants will be provided for the following categories:

- Study disposition (screening / enrollment / start of treatment / end of treatment/EOS)
- Reason(s) for screen failures (on the SCR)

  Note: in case the re-screening resulted in study enrollment, the participant is not considered as a screening failure. In case the re-screening resulted in a screening failure, only the reason for discontinuation related to the re-screening is considered. Screening failures are defined as 'Screen Failure' on the Trial Disposition (Completion/ Discontinuation) eCRF form.
- Reason(s) for premature macitentan discontinuation (on the SS)

  Note: participants specified as "Discontinued" on "Treatment Disposition (End of treatment)" eCRF form.
- Reason(s) for premature study discontinuation (on the Efficacy analysis set).

  Note: participants defined as 'Discontinued' on the Trial Disposition (Completion/ Discontinuation) eCRF form.

5.3. Primary Endpoint Analysis

The primary endpoint is defined as the fold change in PVRI at week 24. PVRI (Wood m^2) is calculated from other pulmonary hemodynamic parameters as below:

$$PVRI(Wood\ m^2) = \frac{mPAP - PAWP}{CI}$$

mPAP: mean pulmonary artery pressure; PAWP: Pulmonary artery wedge pressure; CI: Cardiac index

The formula for PVRI fold change at week 24 is defined as below:

$$\text{PVRI fold change at Week 24} = 100 \times \left(\frac{\text{PVRI at Week 24}}{\text{PVRI at baseline}}\right)$$

PVRI values at baseline and post baseline visits (i.e. Week 24) will be listed based on efficacy analysis set together with the change from baseline and PVRI fold change at Week 24 as defined above.

5.4. Secondary Endpoints Analysis

The secondary endpoints include:

Hemodynamic parameters/ Right heart catheterization	PVR (Wood), mRAP (mm Hg), mPAP (mm Hg), CI (L/min/m^2), CO (L/min), TPR (dyn sec/cm^5), SvO_2 (%)
Functional classification	WHO FC (I, II, III, IV) Panama WHO FC (I, II, IIIa, IIIb, IV)
Exercise capacity	6MWD, Borg dyspnea index (BDI), Borg dyspnea index (BDI)
Biomarker	NT-proBNP
Echocardiography	Tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LVEI)
Quality of Life (QOL)	PedsQL™ 4.0 Generic Core Scales Short Form (SF-15)
Physical activity	Accelerometry

Secondary endpoints listings will be based on efficacy analysis set. Details of these endpoints will be provided in this section.

5.4.1. Hemodynamic Parameters / Right Heart Catheterization

The following pulmonary hemodynamic parameters will be assessed:

Parameter	Definition
PVR (Wood)	Pulmonary vascular resistance $PVR(Wood) = \frac{mPAP - PAWP}{CO}$ $PVR(dyn\ sec/cm^5) = \left(\frac{mPAP - PAWP}{CO}\right) \times 80$
$CO(L/min)$	Cardiac output
$mRAP(mmHg)$	Mean right atrial pressure
$mPAP(mmHg)$	Mean pulmonary artery pressure $mPAP(mmHg) = \frac{(2 \times dPAP + sPAP)}{3}$
$sPAP(mmHg)$	Systolic pulmonary arterial pressure
$dPAP(mmHg)$	Diastolic pulmonary arterial pressure
$dSAP(mmHg)$	Diastolic systemic arterial pressure
$sSAP(mmHg)$	Systolic systemic arterial pressure
$SvO_2(\%)$	Mixed venous oxygen saturation
TPR	Total pulmonary vascular resistance $TPR(dyn\ sec/cm^5) = \left(\frac{mPAP}{CO}\right) \times 80$ $TPR(Wood) = \left(\frac{mPAP}{CO}\right)$

Parameter	Definition
$CI(L/min/m^2)$	Cardiac index $CI(L/min/m^2) = \frac{CO}{BSA}$
$BSA(m^2)$	Body surface area $BSA(m^2) = 0.007184 \times (Weight[kg])^{0.425} \times (Height[cm])^{0.725}$
$PAWP(mmHg)$	Pulmonary artery wedge pressure
$LVEDP(mmHg)$	left ventricular end-diastolic pressure

A listing of Pulmonary Hemodynamic Parameters will be provided. Values at Baseline and Week 24, change from baseline and fold change will be provided. Time point: Baseline, Week 24 and any unscheduled visit.

5.4.2. Functional Classification (WHO FC or Panama FC)

WHO FC is applicable for participants whose age is > 4 years of age when initial informed consent. Panama FC will be assessed for all participants regardless of age.

A listing of WHO functional class and Panama functional class will be provided.

Time points: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52 and any unscheduled visit.

5.4.3. 6-minute Walk Test (6MWT)

6MWT will be conducted in children ≥6 years of age when initial informed consent and who are able to understand and perform the test correctly. The variable of interest is 6MWD expressed as change from baseline to Weeks 24 and 52.

Listings will be provided for measured values and changes from baseline to each timepoint of assessment in 6MWT. Time points: Baseline, Weeks 24 and 52 and any unscheduled visit.

5.4.4. Percent of Baseline in Plasma NT-proBNP

Effect on NT-proBNP will be assessed by percent of baseline at each time point, which is defined as following formula:

$$100 \times \left(\frac{NT\text{-}proBNP\ at\ timepoint}{NT\text{-}proBNP\ at\ baseline}\right)$$

Listings will be provided for the measured values, change from baseline and percent of baseline in NT-pro BNP concentrations at each analysis time point.

Time points: Baseline, Weeks 12, 24, 28, 40, and 52 and any unscheduled visit.

5.4.5. Echocardiography Variables

The echocardiographic variables of interest are tricuspid annular plane systolic excursion (TAPSE) and left ventricular eccentricity index (LVEI). The body surface area (BSA)-normalized TAPSE value will be used instead of the TAPSE value to better account for body growth difference between pediatric subjects and provide a more sensitive description, which is defined as following:

$$normalized\ TAPSE = \frac{original\ TAPSE\ value}{BSA}$$

$$BSA(m^2) = 0.007184 \times (Weight[kg])^{0.425} \times (Height[cm])^{0.725}$$

Listings will be provided for observed values. The percent of baseline at each time point of assessment and absolute change from baseline to each timepoint will be calculated.

Time points: Baseline, Weeks 12, 24, and 52, and any unscheduled visit.

5.4.6. Quality of Life (QoL)

Quality of life will be assessed for participants of ≥ 2 years of age. The Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 questionnaire Generic Core Scales score Short Form (SF-15) will be adapted to assess QoL. SF-15 assesses general physical, emotional, social and school functioning (further details in protocol Appendix 9: Quality of Life assessments). Scoring of dimensions follows:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always) 3-point scales: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child self-report
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0 **Step 2: Calculate Scores** Score by Dimensions: · If more than 50% of the items in the scale are missing, the scale scores should not be computed · Mean scores = Sum of the items over the number of items answered. Psychosocial Health Summary Scores = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Scores = Physical Functioning Scale Score

	Total Score: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% of more items are completed: Impute the mean of the completed items in a scale.

Parent reported QoL data and subject reported QoL data will be listed.

Time points: baseline, Weeks 12, 24, 40, and 52 and any unscheduled visit.

5.4.7. Physical Activity (Accelerometry)

Physical activity will be assessed for participants whose age is ≥ 2 years of age when initial informed consent and measured by accelerometry. The accelerometry variables of interest are:

- Number of hours of daytime activity,
- Mean count per minute of daily activity,
- Mean daily time spent in light physical activity based on a threshold from 800 to 3199 activity counts per minute,
- Mean daily time spent in moderate to vigorous physical activity.

Above variables will be listed. Change from Baseline to every time points of assessment will be calculated. Time points: baseline, Weeks 12, 24, and 52 and any unscheduled visit.

5.5. Exploratory Endpoint(s) Analysis

Exploratory endpoints analyses will be based on efficacy analysis set. Details of these endpoints will be provided in this section.

Participants will be monitored for disease progression events between Day 1 and EOS and disease progression events determined by the Investigator are reported in the "Disease Progression Event" eCRF form.

5.5.1. Time to Disease Progression Event

Note: the protocol wording for this endpoint is time to morbidity/mortality events. For consistency with the CRF and with other macitentan pediatric studies, the wording 'disease progression' is used instead in this document and in the outputs.

Disease Progression event is defined by the occurrence of any of the following events:

- Death (all causes)
- Atrial septostomy or Potts' anastomosis, or registration on lung transplant list

- Hospitalization due to worsening PAH[§]
- Clinical worsening* of PAH defined as:

  Need for, or initiation of new PAH-specific therapy# or IV diuretics or continuous oxygen use AND at least one of the following:

  – Worsening in WHO FC, or

  – New occurrence or worsening of syncope (in frequency or severity as per medical judgment), or

  – New occurrence or worsening of at least two PAH symptoms (ie, shortness of breath/dyspnea, chest pain, cyanosis, dizziness/ near syncope, or fatigue), or

  – New occurrence or worsening of signs of right heart failure not responding to oral diuretics

§ Excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (eg, pneumonia).
***** Worsening from baseline.
# Eg, ERA, phosphodiesterase type 5 (PDE-5) inhibitor, prostanoids, prostacyclin receptor (IP receptor) agonist, soluble guanylate cyclase stimulator

The main reason for disease progression event together with the onset date are reported by the investigator in the eCRF Form 'Disease Progression Event Summary'.

All disease progressions occurring from first study intervention intake until EOS are considered, irrespective of participant's compliance to assigned therapies.

The onset date of the first disease progression event is the earliest of the onset date reported on the 'Disease Progression Event Summary' Form.

Participants who do not experience any disease progression before the EOS have their time to first disease progression right-censored at the time of EOS visit or cut-off date for this interim report, whichever occurs first.

Time to first disease progression is expressed in days and calculated as the onset date of the first disease progression minus date of first study intervention intake plus 1, or, for censored participants, as censoring date minus date of first study intervention intake plus 1.

Date of first disease progression, censoring date and survival time will be provided in listing.

5.5.2. Time to Hospitalization or Death due to PAH

Hospitalization due to PAH is taken from 'Disease Progression Event Summary' Form where 'Hospitalization due to worsening PAH' is ticked.

Death due to PAH is defined as any death with primary cause of death assessed as 'Progressive Disease' on the eCRF Form 'Death Information'.

The onset of the first hospitalization or death due to PAH is the earliest of the onset date of hospitalization due to PAH and death due to PAH.

Time to hospitalization or death due to PAH will be calculated in the same way as described in the time to disease progression. Date of first event, censoring date and survival time will be provided in listing.

5.5.3. Time to Hospitalization due to PAH

Hospitalization due to PAH is defined as in Section 5.5.2.

Time to hospitalization due to PAH will be calculated in the same way as described in the time to disease progression. Date of first event, censoring date and survival time will be provided in listing.

5.5.4. Time to Death due to PAH

Death due to PAH is defined as in Section 5.5.2.

Time to death due to PAH will be calculated in the same way as described in the time to disease progression. Date of first event, censoring date and survival time will be provided in listing.

5.5.5. Time to Death (All Causes)

Time to death (all causes) will be calculated in the same way as described in the time to disease progression. Date of first event, censoring date and survival time will be provided in listing.

5.6. Safety Analyses

Safety listings will be based on the Safety analysis set.

5.6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) last available version at the time of the analysis. The MedDRA version used for reporting AEs will be specified as a footnote in the related outputs.

Treatment-emergent adverse events definition

Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date.

Listings will be provided for all reported AEs with a flag for treatment-emergent AEs. A separate listing of AEs leading to discontinuation of study intervention will be provided.

As per protocol, AEs of special interest include anemia/decreased hemoglobin level, oedema/fluid retention, hepatic impairment, and hypotension. See further details on AESIs in Appendix 8 Adverse Events of Special Interest (AESI). AESIs will be listed separately.

Death information is taken from the "Death Information" form of the eCRF. The primary cause of death is reported on the same form. The original terms used by the investigators to describe the primary death cause are assigned preferred terms for classification and tabulation using the MedDRA dictionary.

A listing of participants who died will be provided. A listing of participants who died due to COVID-19 Infection will also be provided.

5.6.2. Clinical Laboratory Tests

All laboratory data transferred will be taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

Complete hematology tests include:

- Red blood cell count
- Hemoglobin
- Hematocrit
- White Blood Cell count with Differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
- Platelet count.

Complete blood chemistry tests include:

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Total bilirubin
- Direct bilirubin
- Creatinine
- Creatinine clearance
- eGRF
- Blood urea nitrogen (BUN)
- Glucose
- Sodium
- Potassium

- Calcium

Marked laboratory abnormalities are defined as follows:

Table 4: Marked Laboratory Abnormalities

Safety parameter	LL	LLL	HH	HHH
Hematology				
Hemoglobin (g/L)	< 100	< 80	Increase (> 20 g/L) above ULN or above baseline if baseline is above ULN	Increase (> 40 g/L) above ULN or above baseline if baseline is above ULN
Hematocrit (L/L)	< 0.28 F < 0.32 M	< 0.20	> 0.55 F > 0.60 M	> 0.65
Erythrocyte count (10^{12}/L)	NA	NA	NA	NA
Leukocyte count with differential counts (10^9/L)	< 3.0	< 2.0	> 20.0	> 100.0
Platelet count (10^9/L)	< 75	< 50	> 600	> 999
Clinical chemistry				
AST (U/L)	NA	NA	> 3 x ULN	> 5 x ULN
ALT (U/L)	NA	NA	> 3 x ULN	> 5 x ULN
Alkaline phosphatase (U/L)	NA	NA	> 2.5 x ULN	> 5 x ULN
Total bilirubin (µmol/L)	NA	NA	> 2 x ULN	> 5 x ULN
Direct bilirubin (µmol/L)	NA	NA	> 2 x ULN	> 5 x ULN
Creatinine (µmol/L)	NA	NA	> 1.5 x ULN or > 1.5 x baseline if baseline is above ULN	> 3 x ULN or > 3 x baseline if baseline is above ULN
Creatinine Clearance (mL/s)	< 1	< 0.5	NA	NA
Blood urea nitrogen	NA	NA	> 2.5 x ULN	> 5 x ULN
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	> 13.9
Sodium (mmol/L)	NA	< 130	> 150	> 155
Potassium (mmol/L)	< 3.2	< 3.0	NA	> 6.0
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1

Individual participants listings of laboratory assessments will be provided, including change from baseline, with a flag for treatment emergent lab test. In addition, listings will be provided for patients with:

- Any laboratory results outside the normal range
- Any marked laboratory abnormalities
- Hemoglobin decrease from baseline of > 20 g/L
- Liver aminotransferase abnormalities (ie, ALT and/or AST $\geq 3 \times ULN$ and/or TIBIL > 2 × ULN)

5.6.3. Vital Signs and Physical Examination Findings

5.6.3.1. Vital Sign

Continuous vital sign parameters include pulse and blood pressure (systolic and diastolic).

Listings will be produced for all vital signs including change from baseline.

5.6.3.2. Physical Examination

Physical examination parameters include body mass index and growth variables (body weight, and length/height).

BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at the nearest visit will be used in the calculation. In case of equally distant assessments the previous will be chosen.

Listings will be produced for all physical examination parameters, including change from baseline.

5.6.4. Electrocardiogram

The ECG parameters consist of heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB), Fridericia's formula (QTcF).

Bazett's formula: QTcB (msec) = QT (msec) / (RR (msec)/1000)$^{1/2}$;

if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/2}$;

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$;

if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$;

Clinically relevant ECG abnormalities are defined as follows:

Item	Category
QTcB, QTcF measurements	$450 < QTc\ interval \leq 480$
	$480 < QTc\ interval \leq 500$
	$500 < QTc\ interval$
Change in QTcB, QTcF	$30 < change\ from\ baseline \leq 60$
	$60 < change\ from\ baseline$

ECG data will be listed. A listing of clinically relevant ECG abnormalities will also be provided.

5.6.5. PK Concentrations

5.6.5.1. Concentrations of Macitentan and Aprocitentan (Active Metabolite of Macitentan)

Listings will be produced on the PK analysis set for both parameters:

- Concentrations of macitentan
- Concentrations of aprocitentan (active metabolite of macitentan)

5.6.5.2. Trough Concentrations of Macitentan and Aprocitentan (Active Metabolite of Macitentan)

Listings will be produced on the PK analysis set for both following parameters:

- Trough concentrations of macitentan
- Trough concentrations of aprocitentan (active metabolite of macitentan)

5.7. Other Safety Analyses

5.7.1. Extent of Exposure

The extent of study treatment exposure during the study, measured in weeks, is considered in terms of study treatment duration (regardless of treatment interruptions).

Exposure is defined as the time interval between start date of macitentan (see Section 5.1.4) and macitentan EOT date (see Section 5.1.5) inclusive and calculated as: (macitentan EOT date − start date of macitentan +1)/7. For subjects who have not discontinued macitentan permanently at the time of cut-off date, exposure is defined as (cut-off date − start date of macitentan +1)/7.

Macitentan Treatment Log will be listed. The listing will also include exposure.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADaM	Analysis Data Model
AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
BSA	Body surface area
CDISC	Clinical Data Interchange Standards Consortium
CRF	case report form
CSR	Clinical Study Report
DBP	diastolic blood pressure
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
EOS	End of Study
LAP	Left Atrium Pressure
LVEDP	Left Ventricular End Diastolic Pressure
LVEI	left ventricular eccentricity index
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean Pulmonary Arterial Pressure
PAWP	pulmonary arterial wedge pressure
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	Pulse rate
PVR	Pulmonary Vascular Resistance
RHC	Right Heart Catheterization
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SDTM	Study Data Tabulation Model
SMQs	standardised MedDRA queries
TAPSE	tricuspid annular plan systolic excursion
WHO	World Health Organization
WHO FC	World Health Organization Functional Class

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Since the number of subjects included in the analyses of this SAP is expected to be very small, summary outputs will not be provided, instead only listings will be provided.

6.3. Appendix 3 Demographics and Baseline Characteristics

Table 5 presents a list of the demographic variables that will be listed for the Efficacy analysis set.

Table 5: Demographic Variables

Continuous Variables
Age* (months)
Weight (kg)
Height (cm)
Body Mass Index (BMI) (kg/m^2)
Categorical Variables
Age* (newborn infants (<6 months), infants and toddlers (6 months to < 2 years))
Sex (male, female, undifferentiated)
Down Syndrome (Present, Absent)
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported, Unknown, Multiple)
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'
*Age at Day 1 (Visit 2)

Table 6 presents a list of the baseline disease characteristics, including data from the "PAH diagnosis by Right Heart Catheterization (RHC)" eCRF form (when applicable) and from the "Signs and Symptoms of PAH" eCRF form, that will listed for the Efficacy analysis set.

Table 6: Baseline Disease Characteristics

Continuous Variables
BSA-normalized TAPSE (cm/m^2)
LVEI
NT-proBNP
6MWD
Categorical Variables
WHO FC (I, II, III, IV)
Panama FC
PAH etiology (as reported on the 'Etiology of PAH' eCRF Form)
PAH-specific treatment at baseline (None, Beraprost, Sildenafil, Tadalafil, Sildenafil and/or Tadalafil (PDE-5 inhibitor), Ambrisentan, Riociguat, Others)

TAPSE=tricuspid annular plan systolic excursion, LVEI=left ventricular eccentricity index

Both, TAPSE and LVEI are reported on the 'Echocardiography' eCRF Form.

Concomitant PAH-specific medications at baseline are defined as any therapy used on the same day as the first dose of study intervention and might continue after the first dose of study intervention.

Table 7: Baseline RHC

Continuous Variables
Time since PAH diagnosis (days)
Time since RHC in days
mPAP (mmHg)
PAWP or alternative measures of (mmHg)
PVRi (Wood unit x m^2)
LAP (mmHg)
LVEDP (mmHg)

LAP=Left Atrium Pressure, LVEDP=Left Ventricular End Diastolic Pressure, mPAP=mean Pulmonary Arterial Pressure, PAWP=Pulmonary Arterial Wedge Pressure, PVR=Pulmonary Vascular Resistance index,

6.4. Appendix 4 Protocol Deviations

Major protocol deviations and COVID-19 related deviations will be reported in the database.

For efficacy set and PK, a listing of participants with major protocol deviations will be provided as well as a listing with any protocol deviations related to natural disaster / major disruption/ pandemic, including all available details about these deviations.

Between visits, compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as a protocol deviation (see details in Protocol section 6.4).

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications are collected in the 'Concomitant Therapy' eCRF forms and the original (verbatim) terms used by the investigators will be coded using the latest version of WHO Drug code and Anatomic Therapeutic Chemical (ATC) class code dictionaries.

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention.

Study treatment concomitant medications are defined as any therapy used on or after the same day as the first dose of study treatment, including those that started before and continue on after the first dose of study treatment.

Study treatment concomitant medications are derived as any therapy with:

- Start date on or after the Treatment Period start date
- Start date before the Treatment Period start date and end date/time on or after Treatment Period start date/time or end date is missing and the answer to the question "Is the medication/therapy still ongoing?" is 'Yes'.
- Start date is missing and 'Started prior to first study treatment intake' is ticked "Yes" and end date and time on or after the Treatment Period start date/time or end date is missing and the answer to the question "Is the medication/therapy still ongoing?" is 'Yes'.

Imputation rules for missing or incomplete start or end dates are described in Section 5.1.8.

Listings of concomitant medications from baseline and until EOT date + 30 days will be generated on SS. Treatment-emergent concomitant medications will be flagged accordingly. Only listings will display verbatim terms.

6.5.1. PAH-specific Medications

Concomitant PAH-specific medication (Table 8) is defined as any medication/therapy collected on the 'PAH-Specific Treatment' eCRF form with start and end dates as defined in Section 6.5.

Concomitant PAH-specific medications will be listed as defined in Section 6.5 for concomitant medications.

Table 8: PAH-specific Therapies

Class name	**Treatment names**
ERA	ambrisentan, bosentan, macitentan (non study drug)
PDE5-i	sildenafil, tadalafil, vardenafil
Prostanoids	epoprostenol, treprostinil, iloprost, beraprost
IP Receptor agonist	selexipag
sCG stimulator	riociguat
Other	

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

6.6. Appendix 6 Medical History

Participant medical history / current medical conditions present before signing the ICF are recorded in the 'General Medical History' or 'COVID-19 Medical History' eCRF forms.

Separate listings of general medical history and COVID-19 related medical history will be provided.

The original terms used by the investigators to describe diseases/diagnoses are assigned to PTs for classification and tabulation using the latest implemented Medical Dictionary for Regulatory Activities (MedDRA) version PTs will be reported in the participant listings.

6.7. Appendix 7 Intervention Compliance

Dispensed lot numbers will be listed.

Number of tablets returned is not captured in SDTM therefore compliance will only be listed via protocol deviation (Section 6.4).

6.8. Appendix 8 Adverse Events of Special Interest (AESI)

- Anemia:
  - AEs with PT within "Haematopoietic erythropenia (Standardized MedDRA Query [SMQ])",

    or

  - AEs with PT within "Haematopoietic cytopenias affecting more than one type of blood cell (SMQ)" with the exception of two unspecific PTs: "blood disorder",

    or

  - AEs with PT containing the word "anaemia".
- Hepatic disorders:
  - AEs with PT within "Hepatic disorders (SMQ)", excluding the sub-SMQ "Liver-related coagulation and bleeding disturbances"
  - excluding PTs: "Ascites", "Bacterascites", "Biliary ascites" or "Haemorrhagic ascites",
- Hypotension:
  - AEs with PT equal to "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 insipiraory decreased", "CT hypotension complex", "Diastolic hypotension", "Hypotension", "Hypotensive crisis", "Neonatal hypotension", "Dialysis hypotension", "Orthostatic hypotension", "Post procedural hypotension", "Procedural hypotension" or "Mean arterial pressure decreased".
- Symptomatic Hypotension:
  - The case belongs to the Hypotension AMQ (one AE term from the above list) and has a concomitantly reported typical symptom of hypotension ("Circulatory collapse", "Dizziness", "Dizziness postural", "Fall", "Loss of consciousness", "Presyncope", "Shock", "Shock symptom", "Syncope", "Vertigo", "Persistent postural-perceptual dizziness".), i.e., to consider an overlapping period of at least one day between the 2 events (hypotension event and the symptom event e.g., dizziness) OR the case contains an event with any of the MedDRA LLTs equal to "Acute hypotension", "Hypotension paroxysm", "Hypotension symptomatic", "Preshock".
- Edema and fluid retention:
  - AEs with PT within "Haemodynamic oedema, effusions and fluid retention (SMQ)",
  - excluding any PT containing the word "site"
  - Including PT: 'Pulmonary congestion'.

Note: Any modifications of terms (according to the MedDRA SMQs/PTs) may occur based on later dictionary updates; the latest definitions will be used at the time of analyses

7. REFERENCES

Clinical Protocol 67896062PAH3001, Version 5. A multicenter, open-label, Phase III Study to assess the efficacy, safety and pharmacokinetics of macitentan in Japanese pediatric patients (≥ 3 months to < 15 years) with pulmonary arterial hypertension. Janssen Pharmaceuticals K.K. (09 March 2023).