Janssen Pharmaceutical K.K.*

Clinical Protocol

Protocol Title
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

Protocol 67896062PAH3001; Phase 3
Amendment 5

JNJ-67896062 Macitentan

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.; the sponsor is identified on the Protocol Supplementary Information page that accompanies the protocol.

Status: Approved
Date: 7 August 2023
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-RIM-454995, 6.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Confidentiality Statement
The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	7 August 2023
Amendment 4	9 March 2023
Amendment 3	9 March 2022
Amendment 2	25 November 2021
Amendment 1	2 November 2021
Original Protocol	15 October 2021

Amendment 5 (7 August 2023)

Overall Rationale for the Amendment: The main reason for this protocol amendment is to add a database lock (DBL) for Foreign Health Authority interaction.

The updates are indicated in bold for new text and strike-through for deleted text in the following table.

Section number and Name	Description of Change	Brief Rationale
9.4. Statistical Analyses	The sentence is changed as follows: **The SAP for Foreign Health Authority interactions will be finalized prior to the first database lock (DBL) (see Section 9.5).** The SAP will be finalized prior to ~~first~~ **second** DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.	To include data from 2 participants < 2 years in the PIP and CHMP submission.
9.5. Interim Analysis	The sentence is changed as follows: This study plans ~~2~~ **3** database locks (DBLs). 1. **The first DBL will occur when 2 participants < 2 years of age have completed evaluations at Week 24. The dataset at first DBL 24 will be used to support Foreign Health Authority interactions and will be summarized in a separate report.** 2. The ~~first~~ **second** DBL will occur at Week 24 when all participants complete evaluations at Week 24 and both PVRI measurements at baseline and at Week 24 are available with at least 5 participants. The **dataset at second DBL** ~~cutoff dataset at Week 24~~ will be used for the submission **in Japan**. 3. The ~~second~~ **third** DBL will occur at the end of study when all participants complete evaluations at Week 52 and consecutive safety follow-up. The dataset at ~~second~~ **third** DBL will be provided for the long-term safety evaluation during new drug application (NDA) review by PMDA. The SAP will describe the planned interim analyses in greater detail	To include data from 2 participants < 2 years in the PIP and CHMP submission.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Macitentan was approved for the treatment of adult patients with pulmonary arterial hypertension (PAH) in 2015 in Japan, however, is not indicated for pediatric PAH patients in the world. Pediatric indication of macitentan is highly desired because macitentan is the commonly prescribed endothelin receptor antagonists (ERAs) for adult PAH in Japan.

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 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 N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 24	Change from baseline to Week 24 in NT-proBNP
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	Change from baseline to Week 24 in: PedsQL™ 4.0 Generic Core Scales Short Form (SF-15).
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).

Objectives	Endpoints*
To evaluate the long-term effect of macitentan on dyspnea on 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	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	Change from baseline to all assessed timepoints in: PedsQL™ 4.0 Generic Core Scales Short Form (SF-15).
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

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

OVERALL DESIGN

This is a multi-center, open-label, single-arm, Phase 3 study in Japanese pediatric participants (aged between ≥ 3 months and < 15 years), with PAH, to evaluate the efficacy, safety, and pharmacokinetics of macitentan. 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), a non-study specific external expert committee of hepatologists, will be commissioned for this study to review serious hepatic events of special interest.

NUMBER OF PARTICIPANTS

A target of 6 Japanese participants (aged ≥3 months and <15 years) will be enrolled in this study

INTERVENTION GROUPS AND DURATION

Description of Interventions

<table>
<tr><td>Intervention Name</td><td>Macitentan</td></tr>
<tr><td>Type</td><td>Drug</td></tr>
<tr><td>Dose Formulation</td><td>Dispersible Tablet</td></tr>
<tr><td>Unit Dose Strength(s)</td><td>Final market image (FMI) 1.0 mg and 2.5 mg</td></tr>
<tr><td>Dosage Level(s)</td><td>If a participant is ≥2 years old,
<table>
<tr><th>Body weight</th><th>Daily dose</th><th>Combination of tablets (FMI)</th></tr>
<tr><td><15 kg</td><td>3.5 mg</td><td>1 tablet 1.0 mg + 1 tablet 2.5 mg</td></tr>
<tr><td>≥15 kg and <25 kg</td><td>5.0 mg</td><td>2 tablets 2.5 mg</td></tr>
<tr><td>≥25 kg and <50 kg</td><td>7.5 mg</td><td>3 tablets 2.5 mg</td></tr>
<tr><td>≥50 kg</td><td>10.0 mg</td><td>4 tablets 2.5 mg</td></tr>
</table>
If a participant is under 2 years old,
<table>
<tr><th>Age</th><th>Daily dose</th><th>Combination of tablets (FMI)</th></tr>
<tr><td>≥3 months and <6 months</td><td>1.0 mg</td><td>1 tablet 1.0 mg</td></tr>
<tr><td>≥6 months and <2 years</td><td>2.5 mg</td><td>1 tablet 2.5 mg</td></tr>
</table></td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Use</td><td>Experimental</td></tr>
<tr><td>Investigational Medicinal Product (IMP)</td><td>Yes</td></tr>
<tr><td>Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)</td><td>No</td></tr>
<tr><td>Sourcing</td><td>Provided centrally by the sponsor</td></tr>
<tr><td>Packaging and Labeling
(Labels will contain information to meet the applicable regulatory requirements.)</td><td>Child resistant blister packs</td></tr>
<tr><td>Delivery Instructions</td><td>Whole tablet(s) are dispersed in water and administered orally (eg, via spoon, glass, syringe). The full daily dose is taken at a single occasion. Macitentan is administered once daily and irrespective of time of food intake but at approximately the same time of the day. The same administration method should be used as far as possible.</td></tr>
</table>

EFFICACY EVALUATIONS

The following efficacy assessments will be performed during the study:

- Hemodynamic assessments
- Monitoring of disease progression
- Monitoring of signs and symptoms of disease progression
- WHO and Panama functional class
- 6-minute walk test
- NT-proBNP
- Echocardiography
- PedsQL™ 4.0 Generic Core Scales Short Form (SF-15)
- Physical daily activity
- Borg CR10 scale®

PHARMACOKINETIC EVALUATIONS

Venous blood samples of approximately 0.5 mL will be drawn for plasma concentrations of macitentan and aprocitentan. After the macitentan and aprocitentan analysis method for CCI microsampling is validated, CCI microsampling device can be used for blood sample collection. If CCI microsampling device is used for PK sample collection, 0.02 mL or 0.04 mL is needed for blood volume per sample. For individual participants, all points of blood collection should be done using the same sampling method. The timepoints of blood collection will be determined by the age at the start of administration.

For participants ≥2 years old, Visit 3 will take place at steady-state conditions for macitentan and aprocitentan, ie, participants must have received at least 10 days of continuous administration of the same dose of macitentan. The blood samples will be drawn at the following timepoints at Visit 3: predose (immediately before administration of the dose of macitentan study intervention), and at 1, 2, 4, 8, 12, and 24 hours (before macitentan intake the next day) postdose. A trough sample (ie, predose) will be drawn on Week 12 (Visit 6).

For participants <2 years old, the blood samples will be drawn at the following timepoints: 2, 5, and 24 hours (before macitentan intake the next day) postdose on Day 1. A trough sample will be drawn at steady state (Visit 4 and Visit 5).

SAFETY EVALUATIONS

The following safety assessments will be performed during the study:

- AEs
- Physical examination and weight
- Vital signs
- Electrocardiogram
- Hematology, including hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with automated differential, platelet count

- Serum chemistry, including sodium, potassium, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), total and direct bilirubin, alkaline phosphatase (AP), creatinine, and calcium
- Routine urinalysis
- Pregnancy testing

STATISTICAL METHODS

Sample Size Determination

Assuming the true PVRI fold change at Week 24 is 70% and the standard deviation of logarithmic PVRI fold change is 0.50, 5 participants demonstrate 75.4% probability to achieve success criterion. PVRI fold change at Week 24 can be calculated when both measurements, baseline and Week 24, are available. Considering discontinuation of one participant without PVRI assessment of Week 24 during the study, total 6 participants will be defined as the sample size for this study.

Statistical Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Efficacy Analysis Set	All participants who take at least 1 dose of study intervention.
PK Analysis Set	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.
Safety Analysis Set	All participants who take at least 1 dose of study intervention.

PK: pharmacokinetic

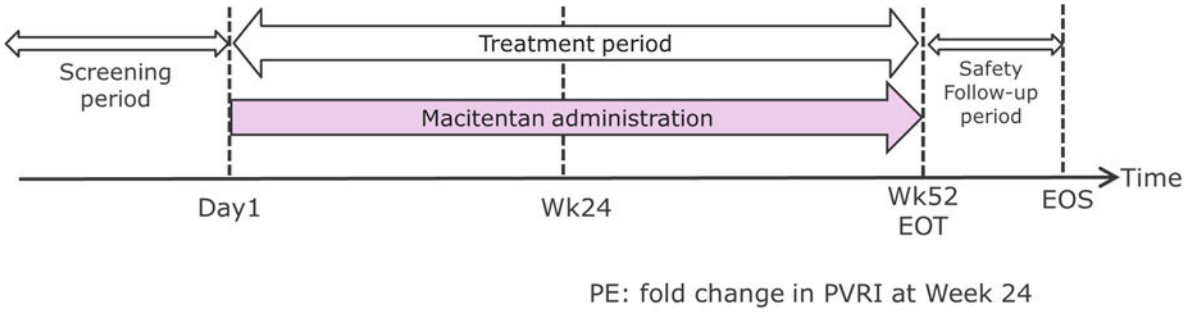
Efficacy endpoints will be summarized over time by descriptive statistics. Descriptive summary statistics, such as n, mean, standard deviation (SD), median, geometric mean, inter quantile range, minimum, and maximum for continuous variables, and counts and proportions for discrete variables, will be used to summarize data. No statistical test will be performed due to the small sample size and insufficient statistical power. Unless otherwise specified, no imputation will be applied to the analysis. The efficacy endpoints will be analyzed using efficacy analysis set. The detailed methods of analysis and the data-handling rules will be provided in the statistical analysis plan.

The safety analysis set is used for the analyses of the safety variables. Adverse events, SAEs, related AEs, AEs by severity and treatment-emergent AEs will be summarized by system organ class (SOC) and preferred term (PT). Descriptive statistics would be provided for all other safety assessments (clinical laboratory parameters, vital signs and ECG parameters).

The PK analysis set will be used for the analyses of macitentan and aprocitentan concentrations.

1.2. Schema

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.

1.3. Schedule of Activities (SoA)

Period	Screening	Treatment											Safety Follow-up
Visit	1	2	3[k]	4	5	6	7	8	9	10	11	12	FU
Timing	Up to 30 days prior to D1	D1	At steady state	W4	W8	W12	W16	W20	W24	W28	W40	W52/ /EOT	30 days after last dose
Visit allowance				± 1 wks	± 1 wks	± 1 wks	± 1 wks	± 1 wks	± 2 wks	± 1 wks	± 1 wks	± 2 wks	+ 7 days
Study Procedure													
Screening/Administrative													
Informed consent[/assent] (ICF) [a]	X												
Demographics	X												
Medical history [b]	X												
Previous/ concomitant therapy	X		X										
Inclusion/exclusion criteria [c]	X												
Study Intervention Administration													
Dispense/administer study intervention		X	X	X	X	X	X	X	X	X	X		
Study intervention accountability	X	X		X	X	X	X	X	X	X	X	X	X
Efficacy Assessments													
RHC	X								X				
6MWT/BDI [d]	X								X			X	
Functional Class (WHO FC/Panama FC) [e]		X		X	X	X	X	X	X	X	X	X	X
Clinical worsening		X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography (TAPSE, LVEI)		X[l]				X			X			X	
Physical activity (Accelerometry) [f]		X				X			X			X	
Quality of Life (SF-15)		X				X			X			X	
Safety Assessments													
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and height	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X[n]				X			X			X	
Clinical Laboratory Tests													
Hematology, chemistry [g]	X	X[o]	X	X	X	X	X	X	X	X	X	X	X
										liver tests monthly [m]			

Period	Screening	Treatment											Safety Follow-up
Visit	1	2	3[k]	4	5	6	7	8	9	10	11	12	FU
Timing	Up to 30 days prior to D1	D1	At steady state	W4	W8	W12	W16	W20	W24	W28	W40	W52/ /EOT	30 days after last dose
Visit allowance				± 1 wks	± 1 wks	± 1 wks	± 1 wks	± 1 wks	± 2 wks	± 1 wks	± 1 wks	± 2 wks	+ 7 days
Study Procedure													
Pregnancy test [WOCBP] [h]	X (serum)	X (urine)		X monthly (urine)								X (urine)	X (urine)
Urinalysis		X		X	X	X	X	X	X	X	X	X	X
Clinical Pharmacology Assessments													
Blood collection for PK assessments (≥2 years old) [i]			X			X							
Blood collection for PK assessments (< 2 years old) [j]		X		X	X								
Pharmacodynamics													
NT-proBNP sampling		X				X			X	X	X	X	
Ongoing Participant Review													
Concomitant therapy		X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AST/ALT=aspartate transaminase/alanine transaminase; BDI=baseline dyspnea index; BP=blood pressure; D=day; ECG= electrocardiogram; EOT=end of treatment; FC=functional class; FU=follow-up; h=hour; ICF=informed consent form; LVEI=left ventricular ejection index; MWT=minute walk test; NT-proBNP=N-terminal pro-brain natriuretic peptide; PAH=pulmonary arterial hypertension; PK=pharmacokinetic; RHC=right heart catheterization; SF=short form; TAPSE=Tricuspid Annular Plane Systolic Excursion; WHO=World Health Organization; W/wk=week; WOCBP=women of child bearing potential.

Footnotes:

a. Must be signed before first study-related activity.
b. Medical history incl. PAH diagnosis/ disease characteristics/demographics
c. Check clinical status again before first dose of study medication.
d. For patients whose age is ≥6 years of age when initial informed consent and who are developmentally able to understand the test and perform 6MWT correctly. Only for patients for whom 6MWT can be done at screening.
e. Both Panama FC and classical WHO FC are assessed. WHO FC is assessed in patients >4 years of age.
f. For patients whose age is ≥2 years of age when initial informed consent. At screening participants will be provided with an accelerometer to be able to capture a baseline profile. Participants who will not prove eligible will return their accelerometer to the study site.
g. For fasting laboratory assessments. Hematology tests include: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with automated differential, and platelet count. Blood chemistry tests include: liver tests [aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin], creatinine and creatinine clearance, eGFR, blood urea nitrogen, glucose, sodium, potassium, and calcium.

h. Serum Pregnancy Testing (for women of childbearing potential only) at the time of screening. Subjects of childbearing potential who are sexually active should be receiving at least 4 weeks of contraception before the urine pregnancy test at Day 1. Monthly urine pregnancy tests for women of child bearing potential to be done at home under parental supervision. In this case the investigator or designee will verify via phone that the test was done and will verify the results. The pregnancy test is done locally.
i. A trough sample (ie, predose) will be drawn on Visit 6 (Week 12). At Visit 3, the blood samples for the PK profiling must be drawn at the following timepoints: Immediately before administration of macitentan (predose) and then 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h (before macitentan intake the next day) postdose. Samples for PK assessment should be collected within 20% deviation from the nominal sampling time.
j. At Day 1, the blood samples for the PK profiling must be drawn at the following timepoints: 2 h, 5 h, and 24 h (before macitentan intake the next day) postdose. A trough sample (ie, predose) will be drawn on Visit 4 and Visit 5. Samples for PK assessment should be collected within 20% deviation from the nominal sampling time.
k. Visit 3 will take place at steady-state conditions for macitentan and its active metabolite (aprocitentan), ie, patients must have received at least 10 days of continuous administration of the same dose of macitentan (patients should take the same dose level and time of day for 11 days prior to Visit 3 including the day of visit). After completion of the 24 hour PK collection, macitentan treatment will begin at the dose determined at Visit 3.
l. Data available within 14 days prior to Day 1
m. For patients of < 2 years, liver tests must be monitored monthly until EOS
n. If there is no change in clinical conditions, data available within 14 days prior to Day1. Not required on Day 1 if screening assessment is performed within 14 days prior to Day1.
o. If there is no change in clinical conditions, data available within 7 days prior to Day1. Not required on Day 1 if screening assessment is performed within 7 days prior to Day1.

2. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and complex disease characterized by vasoconstriction and progressive remodeling of the pulmonary arterial wall. Resulting permanent increase in pulmonary vascular resistance (PVR) eventually leads to right ventricular failure and death. The pathological features are similar in children and adults, but the spectrum of associated conditions, clinical presentation, and factors influencing survival may differ (Ivy 2013).

The definition of PAH in adults and children is the same and is based on pulmonary hemodynamics measured by right heart catheterization (RHC): a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest demonstrates pulmonary hypertension. In patients with PAH, the pulmonary hypertension is pre-capillary and thus they have a normal pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and an elevated PVR > 3 Wood units (WU) (mm Hg/L·min) (Hoeper 2013). In children, PVR index (PVRI) instead of PVR is used in order to account for growth, and PAH is defined as PVRI > 3 WU × m^2 (Ivy 2013; Abman 2015; Hansmann 2016).

There are few epidemiological studies on pediatric PAH in Japan, but according to a nationwide survey on idiopathic PAH/hereditary PAH, the annual incidence is approximately 1 in 1 million people, and it is estimated that children account for approximately 25% of all patients with PAH including adults (Saji 2000). At the end of fiscal 2019, there were 29 PAH patients aged 0 to 19 years who received the intractable disease medical care certificate.

Macitentan (JNJ-67896062) is an orally active, nonpeptide, potent dual endothelin (ET) ET_A and ET_B receptor antagonist characterized by high receptor affinity and a slow receptor dissociation rate. In vitro, macitentan selectively inhibits the binding of ET-1 to ET_A and ET_B receptors as well as the effects mediated by these receptors in functional assays in cells and isolated organs. In vivo, macitentan increases ET-1 plasma concentrations. Macitentan has one active circulating metabolite, aprocitentan, which is also a dual ET_A/ET_B receptor antagonist. In functional in vitro assays (inhibition of contraction of isolated rat aorta and trachea), aprocitentan is, on average, 5-fold less potent than macitentan. However, aprocitentan systemic exposure in humans is about 3-fold higher than macitentan, and aprocitentan contributes to the overall pharmacological effect of macitentan.

Macitentan (OPSUMIT in the United States [US] and the European Union [EU] and ZEPENDO in other regions; 10 mg film coated tablets, once daily) was granted a marketing authorization for the treatment of patients with PAH in the US, European Economic Area (EEA), Canada, Australia, Switzerland, Japan, and additional countries in the Middle East, Asia, and Latin America.

For the most comprehensive nonclinical and clinical information regarding macitentan, refer to the latest version of the Investigator's Brochure (IB) and Addenda for macitentan.

The term “study intervention” throughout the protocol, refers to macitentan as defined in Section 6.1, Study Intervention Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Protocol Supplementary Information, which will be provided as a separate document.

2.1. Study Rationale

Macitentan was approved for the treatment of adult patients with PAH in 2015 in Japan; however, is not indicated for pediatric PAH patients in the world. Pediatric indication of macitentan is highly desired because macitentan is the commonly prescribed endothelin receptor antagonist (ERA) for adult PAH in Japan.

The current management of pediatric PAH by physicians is based primarily on results from studies in adult patients, together with expert recommendations, such as those from the 5th World Symposium for pulmonary hypertension (Ivy 2013). Results from different cohort studies demonstrate that survival rate has been improved in pediatric patients by the use of therapies approved for adult PAH patients (Haworth 2009; Barst 2012; Moledina 2010; Van Loon 2010; Zijlstra 2014). However, treatment remains unsatisfactory, with 5-year survival rates ranging from 71% to 75% (Ivy 2013). These cohort studies before the launch of macitentan indicate that the management of PAH in young patients remains sub-optimal. It is important to address this medical need by making available an efficacious and well-tolerated therapy with an age-appropriate formulation for children with PAH.

The current treatment algorithm for pediatric PAH in Japan is similar to those in the US and Europe. In Japan, various kind of drugs for the treatment of PAH have been approved for children compare to other countries. As of July 2021, 4 drugs (bosentan, sildenafil, ambrisentan, epoprostenol) have been approved for pediatric, and 2 of those 4 drugs (bosentan and ambrisentan) have a same mode of action as macitentan (endothelin receptor antagonist). However, ambrisentan is indicated only for patients aged ≥8 years and not for children aged <8 years. In addition, although bosentan was the first drug approved for pediatric patients in Japan, it has been reported that macitentan tablet for adult is preferred even for pediatric over bosentan pediatric formulation (eg, macitentan does not need monthly liver tests), and number of pediatric PAH patients receiving macitentan as an off-label use exceeds those receiving bosentan (Medical Data Vision [MDV] database).

In order to provide a seamless treatment from pediatric to adult patients also in Japan, it is of significance to develop macitentan, which is commonly prescribed for adults, in pediatric patients in this country.

This study is designed to describe the efficacy, safety, and pharmacokinetics (PK) of macitentan in Japanese pediatric participants with PAH and is being planned to enable pediatric PAH patients to use macitentan in Japan in the future.

2.2. Background

Nonclinical Studies

Available data indicate that nonclinical pharmacology, PK, and available toxicity data support a pediatric development program and supplemental New Drug Application (sNDA).

Safety Pharmacology

Nonclinical safety pharmacology studies did not indicate treatment-related effects, except for a decrease in arterial blood pressure (BP) in cardiovascular studies in dogs.

Toxicology

In repeated-dose toxicity studies, the heart (dog), liver (mouse, rat, dog), and testes (rat, dog) were identified as the main organs affected by treatment with macitentan. Minor or secondary changes were observed in red blood cells, the hemostatic system, thyroid, uterus, and nasal cavities. Macitentan was embryotoxic and teratogenic in developmental and reproductive toxicity studies. It was not genotoxic or phototoxic. Macitentan was not carcinogenic in mice and rats.

In juvenile rats, target organs were not different from those in adult animals. In the pivotal rat juvenile toxicity study at the high dose of 30 mg/kg/day (corresponding to 7-fold the human exposure at 10 mg per day), reduced body-weight gain and low food consumption were noted. Effects on development, such as slight delay of descensus testis, reversible reduction of long-bone length, prolonged estrous cycle, slightly increased pre- and postimplantation loss, decreased mean number of pups, and decreased testis and epididymis weights are considered to be largely secondary to low food consumption and retarded body-weight development. This conclusion was based on literature data showing the correlation between pre- and post-weaning food restriction and delayed onset of puberty and impaired reproductive performance (Almeida 2000; Engelbregt 2002; McGuire 1995). The mean number of sperms with malformed hook was increased in high dose group males, whereas sperm count and motility were unchanged. In two high dose males, testicular tubular atrophy was noted after treatment for 66 days. The no observed adverse effect level was 3 mg/kg/day (TWS Macitentan 2012), corresponding to 1.7-fold the human therapeutic exposure.

Clinical Studies

Pharmacokinetics and Metabolism

For details provided in this section and further information refer to the IB ACT-064922 (Macitentan IB).

Macitentan has a pharmacologically active metabolite (aprocitentan) in humans. In healthy subjects maximum plasma concentrations are generally achieved about 8 h after oral administration of macitentan. Thereafter, plasma concentrations decrease slowly with an apparent terminal half-life ($t_{1/2}$) of approximately 16 h (and 48 h for aprocitentan). After multiple-dose administration steady-state conditions of macitentan are obtained after 3 days (and 7 days for aprocitentan). Macitentan accumulates only minimally (about 1.5-fold), whereas aprocitentan accumulates substantially (about 8.5-fold). For plasma concentrations and other PK parameters measured in Phase 1 studies, refer to the IB (Macitentan IB).

Bioavailability of macitentan and exposure to aprocitentan are unchanged in the presence of food. Thus, macitentan can be taken irrespective of food intake. In adult PAH patients there was no clinically relevant influence of different demographic variables, disease severity, or concomitant

PAH treatment at Baseline on plasma concentrations of macitentan and aprocitentan. Macitentan clearance is mediated by several human P450 enzymes including CYP3A4 and CYP2C9 and is mainly eliminated via the urine (49.7% ± 3.9%). Aprocitentan is approximately 5-fold less potent than macitentan in vitro. However, in humans, systemic exposure to aprocitentan is about 3-fold higher as compared to macitentan, and aprocitentan contributes to the overall pharmacological effect. Formation of aprocitentan is mainly catalyzed by CYP3A4. At the maximum dose of 10 mg planned in this clinical trial, macitentan and aprocitentan are not expected to inhibit cytochrome P450 enzymes or drug transport proteins in the liver or kidney. Neither is it expected that there will be a relevant induction of hepatic CYP3A4. There was no drug-drug interaction between warfarin and macitentan. Concomitant administration of sildenafil has no clinically relevant effect on the PK of macitentan or aprocitentan. Conversely, macitentan's effect on sildenafil exposure is modest and can also be ignored. In the presence of strong inhibitors of CYP3A4 (eg, ketoconazole) and moderate dual inhibitors of CYP3A4 and CYP2C9 (eg, fluconazole, amiodarone) or during co-administration of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors, exposure of macitentan increases whereas potent inducers of CYP3A4 reduce exposure to macitentan. Therefore, these agents should not be used concomitantly with macitentan.

Clinical Safety in Adults

The safety of macitentan was evaluated in the long-term placebo-controlled trial SERAPHIN (AC-055-302) in 742 subjects with symptomatic PAH. The mean treatment duration was 103.9 weeks in the macitentan 10 mg group and 85.3 weeks in the placebo group. Adverse reactions that occurred in at least 10% of the patients (ie, very common) included bronchitis, nasopharyngitis, headache, and anemia. Macitentan 10 mg was associated with a decrease from Baseline hemoglobin levels to below 10 g/dL in 8.7% of patients (as compared to 3.4% in placebo). Common adverse reactions (ie, incidence at least 1% and below 10%) included hypotension, pharyngitis, influenza, and urinary tract infection. Edema and fluid retention, which have been associated with the use of ERAs and are also a clinical manifestation of right heart failure and PAH, had similar frequencies in macitentan 10 mg and placebo groups: 21.9% and 20.5%, respectively (this corresponded to 11.0 events/100 patient-years on macitentan 10 mg vs 12.5 events/100 patient-years on placebo). The incidence of aminotransferase elevations was similar in patients treated with macitentan and with placebo (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >3 × upper limit of normal range [ULN] was 3.4% on macitentan 10 mg and 4.5% on placebo, ALT and/or AST >5 × ULN was 2.5% on macitentan 10 mg and 2% on placebo). Macitentan 10 mg was associated with a decrease in mean count of leukocytes and platelets: incidence on macitentan 10 mg and placebo was 2.5% and 1.6%, respectively, for leukopenia; and 5.0% and 2.8%, respectively, for thrombocytopenia. In the same study, macitentan 10 mg was associated with a decrease in mean leucocyte count from baseline of 0.7×10^9 /L versus no change in placebo-treated patients, and with a decrease in mean platelet count of 17×10^9/L, versus a mean decrease of 11×10^9/L in placebo-treated patients.

Macitentan doses of 150 mg once daily or higher (maximum 300 mg once daily), generating exposures 6 to 10 times higher than those observed with 10 mg once daily, have been used over several months in combination with temozolomide in patients with glioblastoma. These doses were well tolerated, and in particular were not associated with a different safety profile, or with an

increased incidence or severity of known adverse drug reactions for macitentan such as headache, hypotension, liver enzyme elevations, or anemia, compared to 10 mg once daily doses (CSR AC-055-115 2017).

The safety, and tolerability of macitentan in Japanese PAH patients were evaluated in a Phase 2/3 open-label, multicenter study (AC-055-307). Macitentan at a dose of 10 mg per day was well-tolerated in Japanese subjects with PAH. The median (range) duration of study treatment in the Safety set (n = 30) was 839 days (range: 229 to 1037). 100% (30 subjects) had at least one adverse event (AE). Serious adverse events (SAEs) were reported in 30.0% (9 subjects). One subject discontinued study drug due to an AE and eventually died (worsening of pulmonary embolism). The most frequently reported AEs included nasopharyngitis (reported by 21 subjects), headache (14 subjects), diarrhea (10 subjects), epistaxis (9 subjects), flushing (8 subjects), anemia (7 subjects) and contusion (7 subjects).

During the postmarketing experience edema/fluid retention (very common), nasal congestion (common), and hypersensitivity reactions (angioedema, pruritus, rash) (uncommon) have been reported. Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary edema occur when macitentan is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered.

More comprehensive safety data are provided in the IB (Macitentan IB).

Clinical Efficacy in Adults

The efficacy of macitentan in adult patients with symptomatic PAH was evaluated in SERAPHIN (AC-055-302), a multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven, Phase 3 study. In this study, macitentan significantly reduced the risk of the occurrence of morbidity and mortality event. This study was conducted between May 2008 and March 2012 and enrolled 742 subjects randomized in a 1:1:1 ratio to either receive macitentan 10 mg, macitentan 3 mg or placebo allowing the use of PAH-specific background therapy. Macitentan 10 mg reduced the risk for the occurrence of a morbidity/mortality (MM) event with a hazard ratio (HR) of 0.547 versus placebo (97.5% confidence limits [CL] 0.392-0.762, logrank p <0.0001). The HR in the macitentan 3 mg group versus placebo was 0.704 (97.5% CL 0.516-0.960, logrank p=0.0108). Thus the 10 mg dose showed a stronger treatment effect than the 3 mg dose. The treatment effect with macitentan was established early and was sustained for the duration of the study (median duration of treatment of >2 years). Macitentan 10 mg also reduced risk of hospitalization for PAH or PAH-related deaths; HR 0.500 (97.5% CL 0.335-0.747, logrank p<0.0001). The respective HR in the macitentan 3 mg group versus placebo was 0.669 (97.5% CL: 0.462-0.970, logrank p=0.0146). Treatment with macitentan reduced also the number of days in hospital: The mean number of hospitalization days per year (all causes) was 7.5 days in the macitentan 3 mg group and 5.7 days in the macitentan 10 mg group, compared to 12.2 days in the placebo group (Pulido 2013; Macitentan IB).

The efficacy of macitentan 10 mg administered once daily for 24 weeks was evaluated in Japanese PAH patients in a Phase 2/3 open-label, multicenter study (AC-055-307). A total of 30 Japanese patients with PAH were enrolled and received the study drug (macitentan 10 mg). The geometric mean PVR at Week 24 in the per-protocol set (PPS; n = 28) decreased to 60.5% of the baseline level (95% CL: 52.4, 69.9) and the difference from baseline was significant ($p<0.0001$ by the Wilcoxon signed-rank test). The median decrease from baseline to Week 24 was 178 dyn·s/cm^5 (95% CL: −294, −136). At Week 48, mean 6-minute walk distance (6MWD) in the PPS had increased by 62 meters (95% CL: 38, 87) compared to baseline. An increase in Borg dyspnea index was observed at Week 48 (mean of 1.0 [95% CL: 0.4, 1.5] compared to baseline). None of the patients had deterioration in World Health Organization (WHO) functional class (FC) at Week 48. Improvement of WHO FC was observed in 9 (40.9%) out of 22 patients in the PPS at Week 48. Six out of 7 patients with FC III PAH at baseline had improvement to FC II. The geometric mean NT-proBNP at Week 48 in the PPS was 100 pg/mL (95% CL: 54, 183), representing a decrease to 87.7% of the baseline level (95% CL: 62.0, 123.9). At study completion, improvement of 6MWD and WHO FC were maintained in each patient. No patients had deterioration in WHO FC at the end of the study (Macitentan IB).

2.3. Benefit-Risk Assessment

Studies in juvenile rats showed effects mainly during the suckling period (Days 4–21): macitentan exposure was associated with lower food intake, which appeared to be the cause for all other observed differences regarding weight gain and developmental indices. Compared to the toxicity profile known in adult animals, no change in target organ toxicity was identified. Children of at least 2 years of age and adolescents are at a more advanced developmental stage compared to suckling juvenile rats. Adverse event (AE) reports received so far on adolescents and children receiving off-label macitentan have not indicated reduced food intake or delays in general growth or development.

The dose regimens in this study are the same as those in TOMORROW study, which is an ongoing global study in non-Japanese pediatric participants with PAH. Results from the previous clinical studies showed that there was no difference in the efficacy and safety of macitentan between Japanese adults and non-Japanese adults. Also, since there was no ethnic PK difference between Japanese adults and non-Japanese adults up to 10 mg and it is considered that there is no PK difference between Japanese pediatrics and non-Japanese pediatrics, dose regimen rationale for the non-Japanese pediatrics patients is applicable to Japanese pediatric patients (for additional details regarding the justification of dose, see Section 4.3).

Although clinical studies have been performed in children with PAH (eg, bosentan, sildenafil) and other studies are ongoing, current treatment of PAH in children is mostly based on data from clinical trials in adults with PAH.

More detailed information about the known and expected benefits and risks of macitentan may be found in the IB.

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of PAH	The benefit-risk of macitentan in the treatment of PAH has not been established.	Participants will discontinue study intervention if it is not in their best interest or if they need to initiate protocol-prohibited medications including certain biologics (Section 6.8 and Section 7.1). In the presence of PAH-worsening, any PAH specific treatment (PDE5 inhibitor, riociguat, prostanoid) can be initiated per investigator's judgment (Section 6.8.1).
Risks Due to Study Intervention		
Teratogenicity	Teratogenicity was seen in rats and rabbits and is a known class-effect among ERAs. Nonclinical studies in rats revealed that macitentan and its metabolites were excreted into milk during lactation.	Women of childbearing potential who are not using reliable contraception will not be enrolled in the study (Section 5.1 and Section 5.2). Monthly pregnancy tests during treatment with macitentan are recommended to allow the early detection of pregnancy. Women who are pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 4 weeks after the last dose of study intervention will not be enrolled in the study. If a female participant becomes pregnant while on study treatment with macitentan, study treatment must be discontinued (Section 7.1).
Elevations of liver aminotransferases (AST and/or ALT)	Elevations of liver aminotransferases (AST, ALT) have been associated with PAH and with other ERAs. However, in a long-term placebo-controlled study, in PAH, macitentan 10 mg was not associated with increased incidences of treatment-emergent elevations of AST and/or ALT versus placebo.	If unexplained aminotransferase elevations occur and are deemed clinically relevant, or if elevations are accompanied by an increase in bilirubin >2×ULN, or by clinical symptoms of liver injury, macitentan treatment will be discontinued. Reinitiation of macitentan may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not had clinical symptoms of liver injury (Section 7.1.3).

Risks Due to Study Procedures		
Right heart catherization (RHC)	Potential risks associated with RHC include bruising or hematoma, swelling and infection. irritating sensation, heart rhythm abnormalities, low blood pressure, bleeding, general infection, collapsed lung, or clotting of the blood, mortality.	To minimize the risks that may be associated with RHC, the procedure will only be performed at sites experienced with the procedure and complying with specific RHC guidelines.

2.3.2. Benefits for Study Participation

Macitentan is approved for treatment in adult PAH as a 10 mg once daily dose based on a favorable benefit-risk ratio from above stated studies in adults (AC-055-302, AC-055-115, and AC-055-307). Given the similarity of the PAH pathophysiology in adults and children, it is anticipated that treating pediatric patients with PAH with a macitentan dose according to their body weight, targeting a systemic exposure similar to that in adult patients with PAH, will also result in a favorable benefit/risk ratio.

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with macitentan are justified by the anticipated benefits that may be afforded to participants with PAH.

3. 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	Change from baseline to Week 24 in: PedsQL™ 4.0 Generic Core Scales Short Form (SF-15).
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 on 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	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	Change from baseline to all assessed timepoints in: PedsQL™ 4.0 Generic Core Scales Short Form (SF-15).
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.

Refer to Section 8, STUDY ASSESSMENTS AND PROCEDURES for evaluations related to endpoints.

4. STUDY DESIGN

4.1. Overall Design

This is a multi-center, open-label, single-arm, Phase 3 study in Japanese pediatric participants (aged between ≥ 3 months and < 15 years) 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 PAH-specific treatment.

A target of 6 participants will be enrolled in this study. For dosing details, refer to Section 6, STUDY INTERVENTION AND CONCOMITANT THERAPY.

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 posttreatment 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.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

According to International Council for Harmonisation (ICH) E11 (R1) guidelines "Addendum to Guidance on Clinical Trials of Medicinal Products in the Pediatric Population 5.1.1 Use of Extrapolation in Pediatric Development" (ICH E11 Guidelines), clinical data from drugs approved in adults can provide evidence to support their effective and safe use in children for the same indication if the disease course and expected response to the drug can be assumed to be similar between the pediatric and adult populations. In adults, the efficacy and safety of Macitentan in Japanese patients with PAH have already been demonstrated, and PVR and PVRI obtained in the Japanese adult study (AC-055-307) showed improvement similar to that in the non-Japanese adult study (AC-055-302/SERAPHIN).

Similarity of Disease in Adults and Children

PAH in children has been shown to share many similarities with the disease in adults. PAH has a broad spectrum of clinical features in both children and adults that are manifestations of similar processes (Barst 2011; Ollivier 2019). The current management of pediatric PAH is based primarily on results from studies in adult patients, together with expert recommendations, such as those from the 5th and 6th World Symposium for Pulmonary Hypertension (Galiè 2013; Ivy 2013; Rosenzweig 2019). Pediatric consensus treatment guidelines recommend therapeutic algorithms in children based on expert opinion and several studies in children and adults (evidence-based) (Ivy 2013; Abman 2015; Hansmann 2016). Available adult PAH treatments are routinely used in children with PAH according to consensus guidelines. the pathology of PAH are similar between adults and children, and there is no difference in the diagnostic criteria or treatment of PAH between adults and children. Therefore, if the same exposure as that in adults was confirmed in Japanese children in PAH3001 and PVRI tended to improve as in AC-055-307, the results of AC-055-307 could be extrapolated to Japanese children and the efficacy and safety in Japanese children with PAH could be evaluated by reference to the results of the SERAPHIN.

Blinding, Randomization, and Control Group

There will be no blinding, randomization, or control in this study.

Efficacy Measures

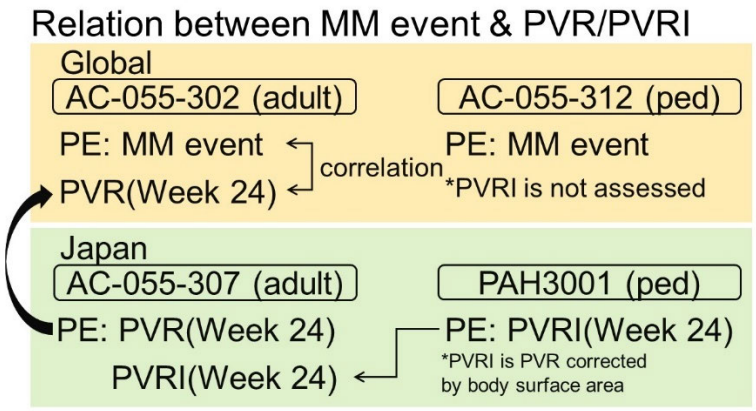
Currently, there are no validated surrogate biomarker endpoints available for PAH in children. Recent treatment guidelines for pediatric PAH patients highlight the need for clinical endpoints measuring long-term outcomes (Ivy 2013). Clinical experts recognize morbidity/mortality event (MM event) as the most clinically meaningful outcomes in PAH (Ivy 2013; Chakinala 2013). A global phase 3 study (AC-055-302, SERAPHIN) in adult PAH patients with macitentan was conducted with the MM event as the primary endpoint (Pulido 2013). As PAH is a progressive disease, MM events are considered to be a more accurate and appropriate endpoint of disease status compared to patient symptom-based endpoints such as 6MWD. At the 4th PAH World Symposium, the MM event was recommended as a clinically meaningful and robust primary endpoint (McLaughlin 2009). On the other hand, in many studies in adult PAH patients, 6-minute walking distance has been defined as the primary efficacy endpoint in clinical trials with short-term follow-up duration of 3 to 6 months (Galiè 2009; Ollivier 2019). Study AC-055-302 (SERAPHIN) is the first clinical study to evaluate long-term outcomes of PAH treatment with MM events as the primary endpoint (Pulido 2013).

PAH is a disease in which the lumen of pulmonary blood vessels is narrowed due to contraction of pulmonary microarteries, thickening of vascular smooth muscle, and proliferation of intima, and PVR is significantly increased. PVR is an objective parameter that reflects right heart load and has been reported to correlate with the prognosis of PAH patients (D'Alonzo 1991; Sitbon 2002). It is used for clinical assessment (D'Alonzo 1991; Barst 2010; Peacock 2009). In addition, a reduction in the risk of MM event occurrence and PVR at 6 months after administration of macitentan was observed in the AC-055-302 (SERAPHIN) study. These results suggest a possible correlation between MM event and PVR (Pulido 2013). The AC-055-307 study with Japanese adult PAH patients defined PVR as the primary endpoint (Tahara 2016). In Japan, it is difficult to conduct a study to evaluate the treatment effect using the MM event from the viewpoint of sample size. The population of Japanese PAH is very small while event-driven study requires a large number of patients.

In assessment of the treatment effect in pediatric PAH patients with PVR, PVRI is usually applied. PVRI is the PVR corrected by the body surface area (Del Cerro 2011; Hansmann 2017). As large individual differences in physique in children, PVRI is generally used for children. In the Japanese pediatric study of bosentan (AC-052-377) (Saji 2018a) and epoprostenol (AC-066A308) (Saji 2018b), the change from baseline in PVRI at 12 weeks after administration was defined as the primary endpoint. Additionally, in the Japanese pediatric study of sildenafil (AC1481298), change from baseline in PVRI at 16 weeks after administration was defined as the primary endpoint.

Figure 2 summarizes the relationship between MM events and PVR/PVRI in the studies of macitentan.

Figure 2: Relationship between MM event and PVR/PVRI



Abbreviations: MM= morbidity/mortality; PE= primary endpoint; PVR= pulmonary vascular resistance; PVRI=pulmonary vascular resistance index

The AC-055-302 (SERAPHIN) study suggests a correlation between MM events and PVR. That is, a decrease in MM events and a decrease in PVR were observed in the macitentan treated group. The correlation between MM events and PVR can be fully explained by the disease mechanism.

Therefore, PVRI is selected as the primary endpoint in this study. Given the lack of previous research data describing a clinically meaningful change in PVRI, an exploratory analysis was performed to quantitate clinically meaningful change in PVRI using the clinical study data with macitentan. Based on this exploratory analysis, it was estimated that it would be clinically meaningful if the point estimate of PVRI fold change (Week 24 to baseline) is equal to or less than 81.6%. For additional details regarding the discussion of clinically meaningful PVRI fold change and the success criterion for this study, please refer to Section 9.2.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants or their legal guardian or legally acceptable representative(s) will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the informed consent/assent form (ICF), the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. For the purposes of this

study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

In the case that the site would like to recruit participants whose parent(s)/legally designated representative cannot read or write, or do not speak or understand the ICF language, additional measures must be implemented in order to ensure participant's rights are respected and the consent obtained is legally valid. If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained. The Contract Research Organization (CRO), the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to the recruitment. The consent process (eg, involvement of an impartial witness) must be fully described, submitted to, and approved by the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB), according to procedures and before such subjects are recruited.

The total blood volume (approximately 65 mL per participant will be collected through Week 52) to be collected.

4.3. Justification for Dose

Dose regimen rationale

Given the similarity of the PAH pathophysiology in adults and children, it is anticipated that treating pediatric patients with PAH with a macitentan dose according to their body weight, targeting a systemic exposure similar to that in adult patients with PAH, will also show efficacy in pediatric patients with PAH. The dose regimens in this study are the same as those in TOMORROW study. TOMORROW study is an ongoing global study in non-Japanese pediatrics with PAH. When multiple doses of macitentan 10 mg once daily were administered to Japanese and non-Japanese healthy adult subjects, there were no major ethnic differences in the PK of macitentan and aprocitentan. There were no major differences in the steady-state trough concentration of macitentan following multiple doses of 10 mg once daily between non-Japanese PAH patients and Japanese PAH patients. Also, it was concluded that there were no major differences in the PK between healthy adult subjects and PAH patients. Therefore, it was considered that even when macitentan was administered to Japanese and non-Japanese pediatric PAH patients at the same dosage and administration, there were no major ethnic differences in the PK. In addition, it was confirmed that the efficacy and safety profiles of macitentan in Japanese PAH patients are not markedly different from those in non-Japanese PAH patients Therefore, the dosage regimen used in this study is identical to that used in TOMORROW study.

Dose regimen rationale for pediatric patients between ≥ 2 years to < 15 years

In order to determine the dosage and administration in pediatric PAH patients, the effect of body weight on clearance and distribution volume was included in a population pharmacokinetic

analysis (PPK) model constructed based on data from adult PAH patients (SERAPHIN study) using allometric scaling factors of 0.75 and 1, respectively, and used as a pediatric PPK model. Since macitentan is mainly metabolized by CYP3A4 and CYP2C9, the metabolic pathway of macitentan is considered to be mature to the same level as that in adults by 2 years of age (Salem F 2014; Koukoulitaki SB 2004), and thus age was not included in the pediatric PPK model. To determine the dosing regimen by body-weight category using the pediatric PPK model, simulations were performed to predict the distribution of macitentan exposure by dosing regimen and body-weight category. For each weight category, dosage was selected to achieve pediatric exposures similar to those in adults following multiple 10 mg once daily doses of macitentan.

When the steady state PK data of 24 pediatric PAH patients in TOMORROW study and the steady-state PK data of 20 adult PAH patients in SERAPHIN study were compared, the mean exposure of macitentan in children was slightly lower than that in adults. Aprocitentan showed similar mean exposures in children and adults. Using the PK data obtained from TOMORROW study, the pediatric PPK model was updated to estimate the steady state AUC at the planned dose in each body-weight category. As the estimated steady state area under the concentration time curve (AUC) was similar to the mean steady state AUC in adults, it was determined that there is no need to change the dosage and administration in TOMORROW study.

AC-055-307 study confirmed the safety and tolerability of the same dosage and administration as in SERAPHIN study (macitentan 10 mg once daily) in Japanese adult PAH patients, and confirmed the efficacy was similar to that in SERAPHIN study. Furthermore, 67896062PAH1005 study, in which Japanese healthy adult participants were treated with multiple doses of macitentan at 75 mg once daily, demonstrated the safety and tolerability at doses up to 75 mg. Therefore, it was considered that the dosage regimen used in TOMORROW Study is acceptable for Japanese as well. Based on the above, the dosage and administration selected in TOMORROW study in children aged ≥2 years can be applied to this study.

Dose regimen rationale for under 2 years pediatric patients

Using the updated pediatric PPK model with the PK data from TOMORROW study, the allometric scaling and clearance in children < 2 years of age was refined. The dose regimen for children below 2 years of age was selected based on the PPK model with a conservative maturation function from Salem et al (Salem 2014) and the body weight from WHO growth chart to avoid excessive systemic exposures. Simulated area under the concentration time curve (AUC) at steady state for the 2 age groups (1 to <6 months and 6 months to <2 years) and for each dose strength (0.5, 1, 2, 2.5, 3 and 3.5 mg) was compared to observed AUC in adults from SERAPHIN-OL and percent of pediatric patients with AUC in [10th, 90th] percentile of adult AUC was assessed. If patients are 1 month to <6 months of age and receive 1 mg, 59.0% of patients can reach [10th, 90th] percentile of adult AUC. If patients are 6 months <2 years of age and receive 2.5 mg, 64.7% of patients can reach (10th, 90th) percentile of adult AUC.

Dose transfer scenario

If a patient becomes 2 years old, he or she will receive macitentan at higher dose (≥3.5 mg) based on the body-weight category (see Table 1).

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit/study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit/study assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at safety follow-up for up to 30 days after last dose of study intervention.

Participants who prematurely discontinue study intervention for any reason before completion of all study visits can be considered to have completed the study if they have completed follow-up.

5. STUDY POPULATION

Screening for eligible participants will be performed within 30 days before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Japanese[1] males or females between ≥ 3 months and < 15 years of age at the first administration of study intervention.

Type of Participant and Disease Characteristic

2. PAH belonging to the Nice 2013 Updated Classification Group 1 (including Down syndrome) and of the following etiologies:

[1] Patient whose parents are Japanese (excluding naturalized Japanese) as verbally reported by the participant or his or her parent(s)/legally designated representative

a. Idiopathic PAH (iPAH)

b. Heritable PAH (hPAH)

c. PAH associated with CHD:

i. PAH with co-incidental CHD

ii. Post-operative PAH (persisting/ recurring/ developing ≥ 6 months after repair of CHD)

d. Drug or toxin induced PAH

e. PAH associated with HIV

f. PAH associated with connective tissue disease (PAH-aCTD)

3. PAH diagnosis confirmed by historical right heart catheterization (RHC; characterized by mean pulmonary arterial pressure ≥25 mm Hg, and pulmonary arterial wedge pressure ≤15 mm Hg, and pulmonary vascular resistance index (PVRi) >4 Wood Units × m^2), where in the absence of pulmonary vein obstruction and/or significant lung disease PAWP can be replaced by left atrium pressure (LAP) or left ventricular end diastolic pressure (LVEDP) (in absence of mitral stenosis) assessed by heart catheterization.

4. WHO FC I to IV.

5. PAH-specific treatment-naïve patients or patients on PAH-specific treatment

Weight

Sex and Contraceptive/Barrier Requirements

6. A woman of childbearing potential must have a negative highly sensitive serum β-human chorionic gonadotropin [β-hCG] test at Screening and a negative urine pregnancy test at the first administration of study intervention.

7. Criterion modified per Amendment 3

7.1 A woman must be (as defined in Appendix 5: Contraceptive and Barrier Guidance)

a. Not of childbearing potential

b. Of childbearing potential and

- Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose - the end of

relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Appendix 5: Contraceptive and Barrier Guidance.

8. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of up to 4 weeks following the EOS.

9. Criterion deleted per Amendment 3.

10. Criterion deleted per Amendment 3.

11. Criterion deleted per Amendment 3.

Informed Consent

12. Parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign an ICF indicating that they understand the purpose of, and procedures required for, the study and is/are willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Informed Consent Process in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

13. Willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

Pulmonary Hypertension related

1. Patients with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease, and/or pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn.

2. Patients with PAH associated with open shunts, as specified below:

    a. Eisenmenger syndrome

    b. Moderate to large left-to-right shunts as judged by the investigator

3. Patients with the following congenital cardiac abnormalities:

a. Cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, pulmonary atresia with ventricular septal defect, unless operatively repaired and with no residual shunt

b. Univentricular heart and/or patients with Fontan-palliation

4. Patients with pulmonary hypertension due to lung disease (eg, bronchopulmonary dysplasia)

Comorbidities related

5. Criterion modified per Amendment 3

5.1 Patients with the following diseases:

a. Patients with pulmonary vein stenosis

b. Patients with bronchopulmonary dysplasia

6. Hemoglobin or hematocrit <75% of the lower limit of normal range (LLN) at Screening.

7. Serum AST and/or ALT >3 × ULN at Screening.

8. Severe hepatic impairment, eg, Child-Pugh Class C, at Screening.

9. Clinical signs of hypotension which in the investigator's judgment would preclude initiation of a PAH-specific therapy at Screening.

10. Severe renal dysfunction with an estimated Glomerular Filtration Rate (eGFR)[2] <30 mL/min/1.73 m^2 at Screening.

11. Known concomitant life-threatening disease with a life expectancy <12 months.

Prior/Concomitant Therapy

12. Patients receiving PAH-specific treatments (excluding PDE-5 inhibitor) at the first administration of study intervention.

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[2] ≥ 2 years and < 15 years ; eGFR = 110.2 x [reference serum Cr (mg/dL) / patient's serum Cr (mg/dL)] + 2.93

≥ 3 months and < 2 years ; eGFR = [110.2 x (reference serum Cr / patient's serum Cr) + 2.93] x *R*

Reference serum Cr: Males = $-1.259Ht^5 + 7.815\ Ht^4 - 18.57\ Ht^3 + 21.39\ Ht^2 - 11.71\ Ht + 2.628$

Females = $-4.536\ Ht^5 + 27.16\ Ht^4 - 63.47\ Ht^3 + 72.43\ Ht^2 - 40.06\ Ht + 8.778$

R = 0.107 x In (age (months)) + 0.656, Ht = body height (m), (Editorial Committee for pediatric CKD 2019)

13. Start or change of dose* with PDE-5 inhibitor within 90 days before RHC at Screening (* Dose adjustments are permitted based on patient body-weight change).

14. Start or change of dose* of Calcium channel blockers and/or diuretics within 7 days before RHC (* Dose adjustments are permitted based on patient body-weight change).

15. Criterion modified per Amendment 4

    15.1 Previous treatment* with macitentan at any time.

    * It is not considered treatment if it does not affect the evaluation of efficacy and safety of this study. In such cases (eg, medical history of short-term macitentan administration), the investigator must contact the sponsor's responsible medical officer to confirm the interpretation is applicable.

16. Any PAH-related surgical intervention planned, or patients listed for organ transplantation related to PAH.

17. Treatment with strong inducers of CYP3A4 (eg, rifabutin, rifampicin, carbamazepine, phenobarbital, phenytoin, St. John's wort), within 4 weeks prior to the first administration of study intervention.

18. Systemic treatment with strong inhibitors of CYP3A4 (eg, clarithromycin, itraconazole, ketoconazole, nelfinavir, posaconazole, ritonavir, and voriconazole) within 4 weeks prior to the first administration of study intervention.

19. Systemic treatment with moderate dual CYP3A4/CYP2C9 inhibitor (eg, fluconazole and amiodarone), or administration of a combination of a moderate CYP3A4 inhibitor (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (eg, miconazole) within 4 weeks prior to the first administration of study intervention.

20. Taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study intervention.

Prior/Concurrent Clinical Study Experience

21. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before the planned first dose of study intervention or is currently enrolled in an investigational study.

22. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 4 weeks after the last dose of study intervention.

23. Criterion deleted per Amendment 3.

24. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Diagnostic Assessments

25. Known allergies, hypersensitivity, or intolerance to macitentan or its excipients.

26. Drug or substance abuse, or any condition that, in the opinion of the investigator, may prevent compliance with the protocol or adherence to study intervention.

27. Previous RHC assessments associated with serious complications, such as (but not limited to) cardiac arrest, arrhythmia requiring intervention, pulmonary hemorrhage, stroke, thromboembolic event, and pulmonary hypertensive crisis.

28. Criterion deleted per Amendment 3.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.3.1. Activity

1. Strenuous exercise may affect study specified assessments and safety laboratory results; for this reason, strenuous exercise should be avoided within 2 hours before all planned study visits and during stays in the study site.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the reason for non-eligibility was transient (eg, abnormal laboratory test, insufficient wash-out period of a forbidden medication). All screening assessments should then be repeated at the time of re-screening. If all re-screening assessments can't be conducted within original screening period, IC should be obtained again and a new patient number should be assigned.

5.5. Criteria for Temporarily Delaying Enrollment or Administration of Study Intervention

Not applicable

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention Administered

Study intervention administration must be captured in the source documents and the case report form (CRF). Study site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

Macitentan will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

For details on treatment in the presence of PAH-worsening, refer to Section 6.8.1, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

The method of administration (eg, spoon) must be recorded in the eCRF.

Table 1: Description of Interventions

<table>
<tr><td>Intervention Name</td><td>Macitentan</td></tr>
<tr><td>Type</td><td>Drug</td></tr>
<tr><td>Dose Formulation</td><td>Dispersible Tablet</td></tr>
<tr><td>Unit Dose Strength(s)</td><td>Final market image (FMI)* 1.0 mg and 2.5 mg</td></tr>
<tr><td>Dosage Level(s)</td><td>If a participant is ≥2 years old,
<table>
<tr><th>Body weight</th><th>Daily dose</th><th>Combination of tablets (FMI)</th></tr>
<tr><td><15 kg</td><td>3.5 mg</td><td>1 tablet 1.0 mg + 1 tablet 2.5 mg</td></tr>
<tr><td>≥15 kg and <25 kg</td><td>5.0 mg</td><td>2 tablets 2.5 mg</td></tr>
<tr><td>≥25 kg and <50 kg</td><td>7.5 mg</td><td>3 tablets 2.5 mg</td></tr>
<tr><td>≥50 kg</td><td>10.0 mg</td><td>4 tablets 2.5 mg</td></tr>
</table>
If a participant is under 2 years old,
<table>
<tr><th>Age</th><th>Daily dose</th><th>Combination of tablets (FMI)</th></tr>
<tr><td>≥3 months and <6 months</td><td>1.0 mg</td><td>1 tablet 1.0 mg</td></tr>
<tr><td>≥6 months and <2 years</td><td>2.5 mg</td><td>1 tablet 2.5 mg</td></tr>
</table></td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Use</td><td>Experimental</td></tr>
<tr><td>Investigational Medicinal Product (IMP)</td><td>Yes</td></tr>
<tr><td>Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)</td><td>No</td></tr>
<tr><td>Sourcing</td><td>Provided centrally by the sponsor</td></tr>
<tr><td>Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)</td><td>Child resistant blister packs</td></tr>
<tr><td>Delivery Instructions</td><td>Whole tablet(s) are dispersed in water and administered orally (eg, via spoon, glass, syringe). The full daily dose is taken at a single occasion. Macitentan is administered once daily and irrespective of time of food intake but at approximately the same time of the day. The same administration method should be used as far as possible.</td></tr>
</table>

* CSF (clinical service form) may be used depending on the results of the FMI stability study

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored in an appropriate, secure area and stored according to the conditions specified on the label.

Refer to the Investigational Product Procedures Manual (IPPM) for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant, must be documented on the intervention accountability form. Participants, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study intervention. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Participants will be provided with a patient diary to record intake at home. Site personnel are to instruct the participant (parent(s)/legally designated representative) to bring the patient diary and any unused macitentan, as applicable, to the site at the beginning of each treatment cycle to check macitentan dosing compliance.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Whenever a participant brings his or her study intervention to the study site for tablet count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the IPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

As this is an open-label study with a single treatment arm, randomization and blinding procedures are not applicable.

6.4. Study Intervention Compliance

Prior to each new dispensation of macitentan, the treatment compliance with macitentan must be evaluated by the site personnel, based on drug accountability, using below formula:

Compliance = [(number of tablets dispensed − number of tablets returned)/Total number of tablets that should have been taken during the visit interval] × 100,

where the visit interval [days], is defined as: current visit date - previous visit date + 1

Treatment interruptions requested by the study investigator are not accounted for in the above formula.

The site personnel must discuss any compliance issue with the parent(s)/caregiver(s) and participant (if developmentally capable) and re-educate them on correct administration of study intervention. Details of such discussion must be documented in the source documents.

If the compliance with study intervention intake is <80% or >120%, it will be considered as a protocol deviation unless it is due to interruption for AE or due to anticipated drug-drug interactions or due to laboratory abnormalities as defined per protocol. Furthermore, the investigator must identify, with the parent(s)/legally designated representative and participant (if developmentally capable), the reasons for this noncompliance and discuss actions to be taken to avoid re-occurrence. This discussion and its outcome must be documented in the source documents.

6.5. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study site personnel (principal or sub investigator unless an immediate safety risk appears to be present).

Macitentan dose adjustments other than for change in age/weight category are not permitted.

Dose adjustments of other PAH-specific medications (see Section 6.8.1) needed due to the participants' change in body weight or due to an AE are performed as per local practice.

6.6. Continued Access to Study Intervention After the End of the Study

This protocol is designed to provide participants with up to approximately 52 weeks of treatment.

No continued access will be proposed for this study as there are 4 approved products in Japan, for the treatment of PAH in pediatric patients. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard of care, if applicable.

6.7. Treatment of Overdose

For this study, any dose of macitentan greater than assigned dose as per the body weight within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific treatment for an overdose. Report to the sponsor in accordance with Section 10.4.4 Special Reporting Situations.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until macitentan can no longer be detected systemically (at least 14 days).
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the electronic case report form (eCRF).

6.8. Concomitant Therapy

Prestudy therapies administered up to 30 days before signing the ICF and PH-specific therapies (ongoing, initiated, or stopped) taken within 90 days of RHC at Screening must be recorded at screening.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include the generic name, start/end dates of administration (as well as whether it was ongoing at start of intervention and/or EOS), route, dose, frequency and indication. Non-therapeutic medications (Drug solution and heparin used for PK blood sampling or right heart catheterization, etc.) do not need to be recorded in the eCRF.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Mandatory Concomitant Therapy

Female patients of childbearing potential who are sexually active must use reliable contraceptive methods until EOS or until the last safety follow-up (whichever occurs latest). If hormonal contraceptives are used, those must be initiated at least 4 weeks before the first administration of study intervention.

For patients who become sexually active any time after the first administration of study intervention and who are of childbearing potential, contraceptive method(s) that are immediately effective must be applied until hormonal contraceptives become effective.

Permitted Concomitant Therapy

Supportive PAH non-specific therapies (eg, diuretics, anticoagulants, oxygen, calcium channel blockers) and changes to such medications are allowed during all study periods. However, the same dose calcium channel blockers and/or diuretics is given for 7 days before RHC (dose adjustments are permitted based on patient body-weight change).

Phosphodiesterase type 5 (PDE-5) inhibitor is the only allowed PAH-specific background medication in this study. If PDE-5 inhibitor is used concomitantly, PDE-5 inhibitor should have been initiated 90 days before RHC in Visit 1 (screening) and the same dose should be maintained until end-of-treatment (EOT). Dose adjustments for PDE-5 inhibitor are permitted based on patient body-weight change.

Use of IV prostanoids for vasoreactivity testing is allowed in all study patients and during all study periods.

Prohibited Concomitant Therapy

To avoid confounding effects, the following treatments are prohibited as specified:

- Use of any investigational drug is prohibited from 4 weeks before the first administration of study intervention and up to EOS.
- Any PAH specific therapy other than PDE-5 inhibitor are prohibited from the first administration of study intervention. Use of macitentan is forbidden in all patients at any time before study entry.
- Use of any PAH-specific background therapy (excluding PDE-5 inhibitor) for the purpose other than PAH worsening.

To avoid drug-drug interactions with macitentan, the following treatments are prohibited as specified:

- Strong inducers of CYP3A4 (eg, rifabutin, rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort) are prohibited from 4 weeks prior to the first administration of study intervention and until EOT

  If they cannot be avoided, their administration should be delayed to after the visits where PK samples are collected and limited to not more than 4 consecutive weeks.
- Systemic administration of strong inhibitors of CYP3A4 (eg, clarithromycin, itraconazole, ketoconazole, nelfinavir, posaconazole, ritonavir, and voriconazole) is prohibited from 4 weeks prior to the first administration of study intervention and until EOT
- Systemic administration of moderate dual CYP3A4/CYP2C9 inhibitor (eg, fluconazole and amiodarone), or combination of a moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (eg,

miconazole) is prohibited from 4 weeks prior to the first administration of study intervention and until EOT.

The administration of ERAs and/or of any investigational drug after the first administration of study intervention must lead to permanent discontinuation of macitentan. The systemic administration of a strong CYP3A4 inhibitor as well as administration of moderate dual CYP3A4/ CYP2C9 inhibitor or a combination of a moderate CYP3A4 and moderate CYP2C9 inhibitor must lead to interruption of macitentan.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.8.1. Rescue Medication

In the presence of PAH-worsening, any PAH specific treatment can be initiated per investigator's judgment. If a participant initiates treatment with ERAs, study intervention (macitentan) must be discontinued (refer to Section 7.1). Clinical PAH worsening defined as:

- 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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation

A participant's study intervention must be permanently discontinued if:

- The participant withdraws consent or assent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant (Refer to Section 8.3.5). The investigator will discuss with the participant and her parent(s)/legally designated representative the appropriate follow-up medical care.
- Noncompliance with study intervention administration defined as compliance rate below 80% in two consecutive visits.
- If a participant initiates treatment with ERAs and/or of any investigational drug (see Section 6.8).

The decision to prematurely discontinue macitentan may be made by the parent(s)/legally designated representative of the participant, the participant (who is developmentally capable to assent), the investigator, or the sponsor personnel. The main reason and whether discontinuation of macitentan is the decision of the participant (ie, parent[s]/legally designated representative, eg, for tolerability or efficacy reasons), the investigator (eg, due to pre-specified macitentan discontinuation criteria, an AE or lack of efficacy), or the sponsor (eg, study terminated) must be documented in the eCRF.

Parent(s)/legally designated representative have the right to prematurely discontinue treatment with macitentan at any time, without any justification. Premature discontinuation of macitentan does not constitute per se a reason to withdraw from the study. In case of premature discontinuation of macitentan, every attempt should be made to keep participants in the study according to the original schedule of assessment. If the parent(s)/legal representative also withdraws the consent to follow the original schedule of assessment as per protocol (premature study visit withdrawal; see Section 7.2), the participant enters the safety follow-up period (see Section 1.3), unless consent is fully withdrawn.

Although parent(s)/legally designated representative do not have to give their reason for prematurely withdrawing their child from the treatment, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

The investigator must discontinue macitentan for a given participant if, on balance, he/she believes that continued administration would be contrary to the best interests of the participant.

Study treatment (macitentan) may be discontinued in response to an AE, a protocol deviation (including eligibility failure, non-compliance with study requirements), for lack of efficacy, for a laboratory abnormality, or for administrative reasons.

Study-specific criteria for discontinuation of macitentan are described Section 7.1.3, Section 7.1.4, and Section 7.1.5, respectively.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will be entered to ensure the protocol-specified number of participants complete the study.

7.1.2. Temporary Discontinuation

Macitentan may be temporarily interrupted in response to an AE, or a laboratory abnormality, or due to anticipated drug-drug interaction. Study-specific criteria for interruption of study treatment are described in Section 7.1.3, Section 7.1.4, and Section 7.1.5, respectively.

If macitentan is interrupted by the participant for any reason, the parent(s)/legally designated representative must immediately inform the investigator.

Interruptions of macitentan must be kept as short as possible and should not exceed 4 consecutive weeks.

For macitentan study treatment interruptions, dose adjustments and the reason for interruption must be recorded in the eCRF.

7.1.3. Liver Chemistry Stopping Criteria

Stopping of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined below or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Interruption of Study Treatment

Macitentan study treatment must be interrupted in the following cases:

- Aminotransferases (ie, ALT and/or AST) ≥3 and <8 × ULN

Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase within 10 days. If AST and/or ALT elevation is confirmed, continue to weekly monitor aminotransferases, total and direct bilirubin, and alkaline phosphatase levels until values return to pre-treatment levels or within normal ranges. If the aminotransferase values return to pre-treatment levels or within normal ranges, re-introduction of macitentan study treatment can be considered.

Re-introduction of macitentan after treatment interruption should only be considered if the potential benefits of treatment with macitentan outweigh the potential risks and when liver aminotransferase values are within pre-treatment levels or within normal ranges. The advice of a hepatologist is recommended.

Liver aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, at 4-weekly intervals during the first 6 months of study treatment, and 12-weekly thereafter.

Permanent Discontinuation of Study Treatment

Macitentan study treatment must be stopped and its re-introduction is not to be considered in the following cases:

- Aminotransferases ≥8 × ULN
- Aminotransferases ≥3 × ULN and associated clinical symptoms of liver injury, eg, nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever)
- Aminotransferases ≥3 × ULN and associated increase in total bilirubin ≥2 × ULN

Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase. Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Other diagnoses (eg, viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (eg, hepatic toxicity of concomitant medication[s] or other substances) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferases abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs (see Section 10.4). All events of aminotransferase ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as a SAE. If these abnormalities are serious hepatic events of special interest, they will be reviewed by an ILSDRB.

7.1.4. Hemoglobin Abnormalities

If there is a decrease in hemoglobin from baseline* of >20 g/L during treatment with macitentan, a retest must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

- Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), peripheral blood smear, reticulocyte count, iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation), lactate dehydrogenase, indirect bilirubin.

Macitentan must be temporarily interrupted if clinically mandated based on the investigator's judgment, or in any of the following situations:

- A decrease in hemoglobin to ≤80 g/L (≤4.9 mmol/L),
- A decrease in hemoglobin from baseline* of ≥50 g/L,
- The need for transfusion.

Re-introduction of macitentan may be considered by the investigator if hemoglobin recovery, defined as a return of hemoglobin above the LLN or to baseline, is achieved.

A decrease in hemoglobin from baseline* of >20 g/L must be recorded as AEs. All hemoglobin abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs.

* Baseline hemoglobin: refers to the last hemoglobin value obtained prior to first intake of macitentan study intervention.

7.1.5. Start of a Strong CYP3A4 Inhibitor / Moderate Dual CYP3A4/CYP2C9 Inhibitors

If any strong inhibitors of CYP3A4 are given, macitentan must be interrupted from first dose of strong CYP3A4 inhibitor and until 4 weeks after the last dose of strong CYP3A4 inhibitor.
If any moderate dual CYP3A4/CYP2C9 inhibitors and/or any co-administration of a combination of a moderate CYP3A4 inhibitor and a moderate CYP2C9 inhibitor are given, macitentan must be interrupted as follows:

- For moderate dual CYP3A4/CYP2C9 inhibitors: from first dose of moderate dual CYP3A4/CYP2C9 inhibitor and until 4 weeks after the last dose of moderate dual CYP3A4/CYP2C9 inhibitor.
- For co-administration of a combination of a moderate CYP3A4 and a moderate CYP2C9 inhibitor: from the first dose of the second co-administered inhibitor and until 4 weeks after last dose of any of the co-administered inhibitors.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent or assent
- Death

Parent(s)/legally designated representative may voluntarily withdraw their child from the study without justification for any reason at any time. The investigator may withdraw a participant from the study (without regard to the participant's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the participant. Withdrawal from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study.

Premature withdrawal from the study happens when parent(s)/legally designated representative and/or participant withdraw the consent to continue the study according to the original schedule of assessments and at the same time prohibit any further data collection. In this case the last visit before full withdrawal of consent constitutes the EOS visit.

Premature discontinuation of macitentan do not *per se* constitute premature withdrawal from the study. Every effort should be made to keep participants in the study as per original schedule of assessments and hence allowing full data collection as per protocol in order to reduce missing data. For these participants the EOS visit will happen 30 days after the last dose.

Premature study visit discontinuation happens if the parent(s)/legally designated representative withdraw the consent to continue the study according to the original schedule of assessments but do not withdraw the consent to provide limited information until the study closure. As a consequence, the participant enters the safety follow-up (See Section 1.3). The date and reason for this premature study visit discontinuation will be reported in the eCRF. The last survival follow-up contact will be used as the EOS.

If premature withdrawal from the study or if premature study visit discontinuation occurs, the reason (if known), along with who made the decision (parent(s)/legally designated representative or participant, investigator, or the sponsor personnel) must be recorded in the eCRF, if known.

If for whatever reason (except death or loss-to-follow-up) a participant is withdrawn from the study, the investigator should make efforts to schedule a last appointment/telephone call to assess the safety and well-being of the participant, collect unused study treatment and discuss follow-up

medical care. Data obtained during this last appointment/telephone call will be recorded in the participants' medical records, but it will not be collected in the eCRF.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent (or assent) then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches) as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. Withdrawal of consent should be an infrequent occurrence in clinical studies (Rodriguez 2015), therefore, prior to the start of the study the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

Circumstances for Reduced Follow-up

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up. These may include (as local regulations permit):

- Less frequent clinical visits
- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to the first dose of the study intervention attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed

lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, quality of life, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: physical and vital sign assessment, blood sample collections for PK and biomarker assessment, blood sample collections for laboratory assessments, efficacy assessment, and study intervention administration. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and/or the eCRF.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 65 mL (Table 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 2: Volume of Blood to be Collected From Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
- Hematology	1.2	13 (for ≥ 2 years)	15.6
		12 (for < 2 years)	14.4
- Serum Chemistry[b]	1.2	13 (for ≥ 2 years)	15.6
		16 (for < 2 years)	19.2
Pharmacokinetic samples (if the regular venous blood sampling is used)	0.5	8 (for ≥ 2 years)	4.0
		5 (for < 2 years)	2.5
Pharmacodynamic/Biomarker samples	1.1	6	6.6
Loss by use of indwelling intravenous cannula	1.0	19	19.0
Approximate Total[c]			60.8 (for participants aged ≥2 years) 61.7 (for participants aged <2 years)

Abbreviations: β-hCG=β-human chorionic gonadotropin; PK=pharmacokinetic.

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Serum chemistry includes serum β-hCG pregnancy tests (for women of childbearing potential only).
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Note: After the macitentan and aprocitentan analysis method for CCI microsampling is validated, CCI microsampling device can be used for blood sample collection. For individual participants, all points of blood collection should be done using the same sampling method. If CCI microsampling device is used for PK sample collection, 0.02 mL or 0.04 mL is needed for blood volume per sample and total volume of blood is the following:

CCI sampler	Participant Age	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total volume of blood for Pharmacokinetic samples (mL)	Approximate total (mL)
10 µL sampler	≥ 2 years	0.02	8	0.16	50.96
	< 2 years	0.02	5	0.10	56.30
20 µL sampler	≥ 2 years	0.04	8	0.32	51.12
	< 2 years	0.04	5	0.20	56.40

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, or sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit, appropriate assessments will be performed based on the judgment of the investigator.

An unscheduled visit must be performed in case of suspected clinical worsening or initiation/dose escalation of PH-specific therapy outside of a regular visit. At unscheduled visits performed due suspected clinical worsening, physical examination, vital signs (blood pressure/pulse rate), weight, laboratory assessments, and WHO FC must be done. Other assessments are done per investigator's discretion. The date of the visit and the reason for the visit, as well as data related to study-specific assessments performed at unscheduled visits, will be recorded in the eCRF.

After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- IPPM
- Laboratory manual
- Quality of life (QoL) questionnaires and QoL completion guidelines
- Electronic data capture (eDC) Manual
- Accelerometer
- Sample ICF
- Sample patient diary
- Additional equipment and information, as needed.

8.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic data to be collected on all participants include: age, sex, race and ethnicity (where local regulations permit), date of the initial PAH diagnosis, PAH disease characteristics, hemodynamic (mPAP, PAWP, PVRI), WHO FC, and Child Pugh Score for participants with known hepatic impairment.

All relevant medical history / current medical conditions based on the investigator's judgment (eg, chronic and ongoing acute conditions, serious past conditions) present before and/or at the time of signing informed consent will be recorded on the medical history page. Where possible, diagnoses and not symptoms will be recorded.

8.2. Efficacy Assessments

8.2.1. Hemodynamic Assessments

The primary efficacy endpoint as well as the secondary endpoints related to hemodynamic parameters are described in Section 3, OBJECTIVES AND ENDPOINTS.

Pulmonary arterial catheters will be placed in all participants enrolled. Participants will consent to have the catheter inserted for the purposes of the study. Catheter placement may be confirmed by chest X-ray or fluoroscopy, as clinically indicated. All effort will be made to minimize radiation exposure time.

If an RHC was performed in the 60-day period prior to the first administration of study intervention, and the criteria for historical RHCs defined in Appendix 6: Sponsor Heart Catheterization Guidance are met, the RHC does not need to be repeated at Screening. If PDE-5 inhibitor is used concomitantly, PDE-5 inhibitor must be stable for at least 90 days prior to the baseline RHC.

It is to keep the dose of calcium channel blockers and/or diuretics stable for 7 consecutive days prior to the Screening- and Week 24 RHC.

Hemodynamic parameters measured and collected in the eCRF include heart rate, PAWP (or LVEDP), mRAP, systolic/diastolic pulmonary artery pressures (sPAP/dPAP), systolic/diastolic systemic arterial pressure (s-, d-SAP), SvO_2 and CO.

Calculated hemodynamic parameters:

Parameter	Definition
PVRI (pulmonary vascular resistance index)	$PVRI(Wood\ m^2) = \frac{mPAP - PAWP}{CI}$ $PVRI(dyn\ sec\ \ m^2/cm^5) = \left(\frac{mPAP - PAWP}{CI}\right) \times 80$
PVR (pulmonary vascular resistance)	$PVR(Wood) = \frac{mPAP - PAWP}{CO}$ $PVR(dyn\ sec/cm^5) = \left(\frac{mPAP - PAWP}{CO}\right) \times 80$
CO (cardiac output)	$CO(L/min)$
mRAP (mean right atrial pressure)	$mRAP(mmHg)$
mPAP (mean pulmonary artery pressure)	$mPAP(mmHg) = \frac{(2 \times dPAP + sPAP)}{3}$
sPAP (systolic pulmonary arterial pressure)	$sPAP(mmHg)$
dPAP (diastolic pulmonary arterial pressure)	$dPAP(mmHg)$
dSAP (diastolic systemic arterial pressure)	$dSAP(mmHg)$
sSAP (systolic systemic arterial pressure)	$sSAP(mmHg)$

Parameter	Definition
SvO_2 (mixed venous oxygen saturation)	$SvO_2(\%)$
TPR (total pulmonary vascular resistance)	$TPR(Wood) = \left(\frac{mPAP}{CO}\right)$ $TPR(dyn\ sec/cm^5) = \left(\frac{mPAP}{CO}\right) \times 80$
CI (cardiac index)	$CI(L/min/m^2) = \frac{CO}{BSA}$
BSA (body surface area)	$BSA(m^2) = 0.007184 \times (Weight[kg])^{0.425} \times (Height[cm])^{0.725}$
PAWP (pulmonary artery wedge pressure)	$PAWP(mmHg)$
LVEDP (left ventricular end-diastolic pressure)	$LVEDP(mmHg)$

The clinical sites will use their local operating procedures for the insertion, maintenance, and removal of the catheter. The participant will then be monitored for a minimum of 20 hours or until discharge.

8.2.2. Monitoring of disease progression

The secondary endpoints are related to disease progression and are described in Section 3. In order to assess these endpoints, the following data are collected:

- Death, primary cause and date of death will be collected on a dedicated eCRF page.
- PAH-related non-pharmacological interventions (such as atrial septostomy, etc.) and the date and reason for the intervention are reported on a dedicated eCRF page.
- Medications related to PAH (such as PAH-specific medications, diuretics, and oxygen) are recorded on the eCRF page for previous/concomitant medications (refer to Section 6.8).
- For hospitalizations, the admission/discharge date together with the reason for hospitalization is recorded on either the AE eCRF page or on the dedicated eCRF page (if cause is related to PAH).
- Signs/symptoms denoting PAH worsening together with their onset/resolution date as well as WHO FC are recorded on dedicated eCRF pages and as specified in Section 8.2.2.

The investigator (or delegate) will describe the condition of the participant at baseline (ie, at Visit 2) in a narrative. In the presence of disease progression, the investigator (or delegate) will provide an additional narrative to document worsening in the participant's condition.

8.2.2.1. Signs and Symptoms of PAH

In order to standardize assessment of disease progression, investigators will verify the presence/absence of predefined signs and symptoms denoting clinical worsening of PAH.

The presence and absence of signs/symptoms is recorded on a dedicated eCRF page. The date of new onset or worsening is also recorded in the eCRF.

If there is syncope or at least 2 new or worsening signs/symptoms the investigator reports disease progression on a dedicated eCRF page and performs further exams to determine the cause

8.2.2.2. Functional Class

The WHO FC (Appendix 7: WHO Functional Class) and the Panama FC (Appendix 8: Panama Functional Class for Pediatrics) are recorded in the eCRF. The Panama FC is tailored for children up to 16 years of age (Lammers 2011). When applicable, WHO FC and the Panama FC must be performed before the 6MWT.

Worsening of the clinical condition of a participant can occur at any time during study participation. Parent(s)/caregiver(s) will be instructed to contact the investigator immediately if the participant deteriorates to arrange for a visit if needed.

In the presence of suspected disease progression event (eg, signs/symptoms denoting PAH worsening or deterioration of WHO FC, the investigator will determine the main and contributing causes for worsening as per local practice. If applicable, the investigator reports which components of the primary efficacy endpoint are met. The onset date of worsening, the main and contributing cause(s) for worsening are recorded on dedicated eCRF pages ("Disease Progression Event Summary", "Disease Progression Event page", and if applicable "Clinical Worsening"). If the disease progression fulfills the seriousness criteria (eg, needs hospitalization), the event must also be reported as an SAE within 24 hours of the investigator's knowledge that the event is serious using an SAE reporting form.

Contributing causes other than PAH are also reported as AE or SAE, as appropriate.

8.2.3. 6-Minute Walk Test

The 6MWT is a non-encouraged test that measures the distance covered by the participant during a 6-minute walk. Guidelines are provided in Appendix 10: Sponsor 6-minute Walk Test Guidance.

The 6MWD will be assessed in participants ≥ 6 years of age when initial informed consent and who understand and are able to perform the test correctly (Douwes 2016; Takatsuki 2013). Test results and the date and time of assessment will be recorded in the eCRF. If a participant wears a mask during the 6MWT this will be entered in the source document but not in the eCRF.

8.2.4. NT-proBNP

Venous blood samples of approximately 1.1 mL will be collected for measurement of NT-proBNP at baseline (predose), and at Weeks 12, 24, 28, 40, and 52.

The quantification of NT-proBNP plasma levels will be performed by the central laboratory.

The material required for NT-proBNP sampling will be provided to the investigational site before the start of the study. The procedure for collection and analysis of NT-proBNP is described in the respective Laboratory Manual. Plasma samples are stored in an upright position at −18°C or at cooler temperature.

8.2.5. Echocardiography

Left ventricular eccentricity index and TAPSE will be assessed.

Left Ventricular Eccentricity Index (LVEI): For this index the independent reviewer will measure, and record in mm with up to one decimal place, the following LV internal diameters, using the parasternal short axis view at the level of the papillary muscles.

- D1: LV internal diameter perpendicular to interventricular septum at end-diastole
- D2: LV internal diameter parallel to interventricular septum, and at right angle from D1, at end-diastole
- S1: LV internal diameter perpendicular to interventricular septum at end-systole
- S2: LV internal diameter parallel to interventricular septum, and at a right angle from S1, at end-systole

The LVEI is a ratio that will be calculated by Sponsor as follows:

- $LVEI_{diastole} = D2/D1$
- $LVEI_{systole} = S2/S1$

Tricuspid Annular Plane Systolic Excursion (TAPSE): TAPSE is a dimension used to evaluate Right Ventricle (RV) longitudinal systolic function; it measures the extent of systolic motion of the lateral portion of the tricuspid ring towards the apex. To obtain an appropriate M-Mode recording to be used for TAPSE measurement, 2D imaging of the apical four-chamber view will allow for correct placement of the M-Mode cursor through the tricuspid lateral annulus. TAPSE, recorded in mm with up to one decimal place, is the linear dimension between the positions of the tricuspid valve annulus at end-diastole and endsystole.

The investigator (or delegate) will submit generated echocardiography data (TAPSE, D1, D2, S1, and S2) in eCRF.

8.2.6. Physical activity

Physical daily activity assessed by accelerometry has been shown to correlate with 6MWD in adult PAH patients and is significantly lower in patients with WHO FC III/IV as compared to WHO FC I/II. Furthermore, PAH patients with daytime activity <15 h/day had shorter transplant-free survival (Kaplan-Meier estimate) as compared to patients with longer daytime activity. Thus, physical activity measured by accelerometry may be used as a tool to assess functional capacity, disease severity, and prognosis in patients with pulmonary hypertension (Pugh 2012; Ulrich 2013). Accelerometry is being used in children excluding infants for indications other than PAH (Cliff 2009; Robertson 2011; Van Cauwenberghe 2001). Since 6-minute walk test cannot reliably be assessed in children with PAH (Adatia 2013), physical activity by accelerometry may be a potential tool to assess functional capacity in this population. No data exist so far in children with PAH and thus change in physical activity will be assessed as an exploratory endpoint in this study.

The physical activity [counts/min] of the participant is assessed via accelerometer. The participant collects data wearing the accelerometer for 10 to 14 consecutive days before respective visits [refer to Schedule of Activity]. If, for any reason, data are not collected before respective study visits, the participant will collect the data during the 10 to 14 days following the visit. For Screening, the physical activity must be collected any time during Screening and before Visit 2. This will allow collecting data during weekdays and weekend days and will provide a reliable estimate of the usual physical activity of the participant.

At Visit 1 (screening), participants, whose age is ≥2 years of age when initial informed consent, will be provided with an accelerometer to be able to capture a baseline profile, and the investigator (or delegate) instructs parent(s)/legally designated representative and developmentally capable participants on how and when to wear the accelerometer (refer to Sponsor Accelerometry Guidelines). Participants will be asked to continuously wear the device on the non-dominant wrist or hip worn or ankle worn. The accelerometer is worn during the waking hours of the participant. The device may be removed during the night rest and during activities when the device could get wet (eg, showering, bathing, swimming).

The data is transferred to the accelerometry central laboratory as instructed in the Sponsor Accelerometry Guidelines. Participants who will not prove eligible will return their accelerometer to the study site, but whose data (if collected during Screening) are transferred to the central lab. At Visit 12 the accelerometer will not be returned to the participant. After successful data transfer the device is re-set and can be re-used by another study participant.

The central laboratory will read daily counts/min and will analyze duration of daytime activity and time [minutes] spent in moderate-to-vigorous physical activity (MVPA) as compared to time spent in sedentary, light, moderate, vigorous physical activity. These data are transferred to the sponsor. Sites and participants will not have access to data generated from the use of the device during the study. All devices will be collected at the final visit and inventoried.

8.2.7. Borg CR10 Scale®

CCI [redacted]

8.3. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.4, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.3.1. Physical Examinations

Weight and height of the participants will be measured at each visits until the end of the treatment. The dose of macitentan should be adjusted as per the body weight as referred in Section 6.

Physical examination at screening includes the examination of the general appearance, cardiovascular, respiratory, gastrointestinal, skin, eyes, ears, nose, throat, lymph nodes, nervous system. At subsequent visits, physical examination includes the examination of general appearance, cardiovascular, and respiratory system.

Other exams will be performed if indicated, based on medical history and/or signs and symptoms.

Information for all physical examinations must be included in the source documentation at the study site. If an abnormality is found, it should be specified on the corresponding eCRF page (except for abnormalities related to PAH worsening), describing the diagnosis (eg, pneumonia) and not the signs related to the abnormality (eg, fever, coughing, dyspnea). Clinically relevant findings (other than those related to PAH worsening) that are present prior to signing of informed consent must be recorded on the Medical History eCRF page. Physical examination findings made after signing of informed consent, which meet the definition of an AE (Section 10.4.1), must be recorded on the AE page of the eCRF.

Signs and symptoms related to PAH are not reported together with the physical examination findings but on dedicated eCRF pages.

8.3.2. Vital Signs

Systolic and diastolic Blood pressure (BP) and heart rate will be assessed. Vital signs are measured non-invasively.

Blood pressure and heart rate measurements will be assessed in supine, sitting or standing positions with a completely automated device. Manual techniques will be used only if an automated device is not available. In addition, throughout the study BP is tried to be measured on the same arm and in the same position (supine, sitting or standing), using the same device by the same operator throughout the study for an individual participant.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Vital signs are recorded in the eCRF.

8.3.3. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB), QT corrected according to Fridericia's formula (QTcF).

$$QTcB = \frac{QT(msec)}{(RR(msec)/1000)^{1/2}}$$

$$QTcF = \frac{QT(msec)}{(RR(msec)/1000)^{1/3}}$$

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Appendix 2: Clinical Laboratory Tests . The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

A central laboratory will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. If the results from the central laboratory are not available in time for enrollment of the participant, the results from the local laboratory may be used for eligibility verification. The results with the corresponding normal ranges must be recorded in the eCRF.

Clinically relevant laboratory findings that are known at the time of signing of informed consent must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities detected after signing of informed consent must be reported as an AE or SAE, as appropriate.

In all patients, laboratory tests must be monitored monthly for the first 6 months of study period and at each scheduled visit (every 12 weeks) until EOS. In addition, for patients of < 2 years, liver tests must be monitored monthly until EOS.

8.3.5. Pregnancy Testing

Urine pregnancy tests for women of childbearing potential can be done at home under parental supervision at every month. The investigator (or delegate) will verify via phone that the test was done and will verify the results.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

If a female participant becomes pregnant while on study intervention with macitentan, study intervention must be discontinued (refer to Section 7.1). The investigator must counsel the participant and the parent(s)/legally designated representative and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. This counseling comprises all medications administered at that time and follows instructions of the respective approved drug labels.

Any pregnancy occurring in female participants or partners of male participants after study start (ie, signing of informed consent) up to 4 weeks following EOS must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Pregnancy Notification form, which is sent to the CRO (see contact details provided on the respective Pregnancy form), and on an AE page in the eCRF, if occurring up to EOS or up to the safety follow-up telephone call (whichever is last). The CRO will provide Pregnancy forms to the sponsor.

Any pregnancy must be followed up to its conclusion and the outcome must be reported to the CRO on the End of Pregnancy – Collection Form B and on the Product Exposure During Pregnancy – Collection Form A.

Any AE associated with the pregnancy and occurring up to EOS or up to the safety follow-up telephone call (whichever is last) must be reported on a separate AE page in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE reporting form.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQCs can be found in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs, as well as PQCs, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or

sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.4.5. Pregnancy

Pregnancy is associated with maternal mortality in patients with PAH (Bédard 2009) and may hence confound the efficacy and safety of macitentan. Furthermore, a teratogenic effect of macitentan cannot be excluded. Therefore, female participants of childbearing potential who are sexually active must use a reliable method of contraception (refer to Appendix 5: Contraceptive and Barrier Guidance).

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.4.6. Adverse Events of Special Interest

Adverse events of special interest in this study are:

- Anemia/Decreased hemoglobin level
- Edema/Fluid retention
- Hepatic impairment/ ALT and/or AST increase
- Hypotension

A **possible Hy's law case** is defined by the occurrence of ALT and/or AST ≥3 x ULN, alkaline phosphatase <2 x ULN together with total bilirubin ≥2 x ULN or INR >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor in an expedited manner using the SAE reporting form, even before all other possible causes of liver injury have been excluded (FDA 2009).

A confirmed Hy's law case must be reported as a SAE.

Refer to Section 7.1 for the management of liver aminotransferases and/or hemoglobin abnormalities.

8.5. Quality of Life Assessments

CCI [redacted]

[redacted]

8.6. Pharmacokinetics

Plasma or blood samples will be used to evaluate the PK of macitentan and aprocitentan. Plasma or blood collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma or blood samples. Participant confidentiality will be maintained.

8.6.1. Evaluations

Venous blood samples of approximately 0.5 mL is needed for plasma concentrations of macitentan and aprocitentan. After the macitentan and aprocitentan analysis method for CCI microsampling is validated, CCI microsampling device can be used for blood sample collection. For individual participants, all points of blood collection should be done using the same sampling method. If CCI microsampling device CCI is used, peripheral blood samples of approximately 0.02 mL or 0.04 mL is needed for blood concentrations of macitentan and aprocitentan. The total of volume of blood samples drawn for PK assessments would be 0.16 mL to 4.0 mL for participants aged ≥2 years and 0.10 mL to 2.5 mL for participants aged <2 years (Refer to Section 8). The timepoints of blood collection will be determined by the age at the start of administration.

For participants ≥2 years old, Visit 3 will take place at steady-state conditions for macitentan and aprocitentan, ie, participants must have received at least 10 days of continuous administration of the same dose of macitentan. The blood samples will be drawn at the following timepoints at Visit 3: predose (immediately before administration of the dose of macitentan study intervention), and at 1, 2, 4, 8, 12, and 24 hours (before macitentan intake the next day) postdose. A trough sample (ie, predose) will be drawn on Week 12 (Visit 6).

For participants <2 years old, the blood samples will be drawn at the following timepoints: 2, 5, and 24 hours (before macitentan intake the next day) postdose on Day 1. A trough sample will be drawn at steady state (Visit 4 and Visit 5).

The date and exact actual clock time of each blood sample draw will be collected. In addition, the last dosing date and time of macitentan intake before and after blood PK sampling will be collected in the eCRF.

8.6.2. Analytical Procedures

Pharmacokinetics

Plasma or blood samples will be analyzed to determine concentrations of macitentan and aprocitentan using a validated, specific, and sensitive liquid chromatography coupled to mass spectrometry method by or under the supervision of the sponsor. If the regular venous blood sampling method is used, plasma samples will be analyzed. If CCI microsampling device is used, blood samples will be analyzed. The foreseen limit of quantification (LOQ) in plasma and blood for macitentan and aprocitentan is 1 ng/mL. Details of LOQ will be provided in the SAP.

If required, some plasma or blood samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be

stored for future analysis of other co-administered treatments and protein binding, and the metabolite profile.

8.6.3. Pharmacokinetic Parameters and Evaluations

Based on the individual plasma or blood concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of macitentan and aprocitentan will be derived using population PK modelling. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant.

Plasma or blood PK parameters of macitentan and aprocitentan will be derived by noncompartmental analysis of the plasma or blood concentration-time profiles (for participants aged ≥2 years only).

Subjects ≥2 years of age:

- Trough concentrations of Macitentan and aprocitentan at Week 12
- Macitentan and aprocitentan concentration at predose, postdose 1, 2, 4, 8, 12, and 24 hours at steady state (after at least 10 days of dosing at the same dose), (PK profile over 24 hours at predose and following administration of macitentan during steady-state conditions)
- Maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), and AUC_{τ} of Macitentan and aprocitentan at steady state, These PK parameters will be derived noncompartmental analysis of the plasma or blood concentration- time profile.

  AUC_{τ} will be calculated according to the linear trapezoidal rule using the measured concentration-time values above the LOQ during one dosing interval.

Subjects <2 years of age:

- First day of dosing: Macitentan and aprocitentan concentration at 2, 5, and 24 hours postdose.
- At Week 4 and Week 8 (steady state): Predose Macitentan and Aprocitentan concentrations
- Apparent clearance and volume of distribution from PPK.

The PPK plan and the PPK report will be prepared separately from this study protocol.

8.7. Genetics and Pharmacogenomics

Pharmacogenomics or genetics are not evaluated in this study.

8.8. Immunogenicity Assessments

Not Applicable.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

Formal statistical hypotheses testing is not planned for this study. Primary objective of this study is to assess the effect of macitentan on hemodynamic measures in Japanese pediatric participants with PAH in terms of geometric mean of fold change in PVRI. Refer to Section 4.2 for additional details.

9.2. Sample Size Determination

In order to calculate sample size, success criterion in this study was defined. The success criterion is closely related to the sample size. Therefore, in this section, discussion on the success criterion is provided prior to the discussions on sample size and probability of success.

Clinically Meaningful PVRI Fold Change and Success Criterion

PVRI is selected as the primary endpoint in this study, in which macitentan is administered to Japanese pediatric PAH patients. A literature survey was conducted to identify if there were any previous research describing clinically meaningful fold change in PVRI. However, no relevant literature could be found. With the pre-definition of clinically meaningful fold change in PVRI, it would be straightforward to interpret the study results of PAH3001. Thus, an exploratory analysis was performed to quantitate clinically meaningful changes in PVRI using the clinical study data with macitentan.

Macitentan 10 mg is currently approved for adult PAH patients both in Japan and global. An exploratory analysis of PVRI was performed using the placebo and macitentan 3 mg and 10 mg groups data in the global Phase 3 study (AC-055-302 study, SERAPHIN) (Pulido 2013). The analysis results suggested the clinically meaningful fold change in PVRI because PVRI was found to correlate with MM events. Table 3 shows the analysis results of fold change in PVRI at 24 weeks after administration. From the individual patient data of 187 subjects who participated in the PK/pharmacodynamic (PD) study of AC-055-302, the analysis was conducted with 145 patients excluding the patients who have imputation for missing values.

Table 3: PVRI Fold Change of Week 24 to Baseline (AC-055-302)

PVRI (Wood m^2)	Placebo (n=68)	Macitentan 3mg (n=62)	Macitentan 10mg (n=57)
Analysis set[1)]	50	47	48
Baseline			
Mean (SD)	19.8 (12.48)	21.4 (11.75)	19.8 (11.39)
Median	17.1	19.2	18.6
Min, Max	6.0, 65.6	6.0, 50.0	6.2, 51.3
Week 24			
Mean (SD)	23.1 (13.85)	16.8 (9.73)	14.7 (9.96)
Median	22.0	14.8	12.0
Min, Max	4.4, 65.7	1.7, 54.7	3.2, 54.0
Change from baseline at Week 24			
Mean (SD)	3.4 (7.64)	-4.6 (6.29)	-5.1 (8.34)
Median	1.2	-3.3	-3.9
Min, Max	-7.1, 24.8	-25.2, 4.6	-30.5, 13.9
[95%CI]	[1.18, 5.52]	[-6.48, -2.79]	[-7.50, -2.65]
Fold change (%)[2)]			
Geometric mean [95%CI]	115.7 [104.6, 127.8]	77.0 [69.9, 84.7]	71.4 [62.5, 81.6]

1) Patient who participated in the PK/PD study (All randomized set) and excluded the patient who have imputation for missing values; 2) (Postdose value/predose value) x 100

Abbreviations: CI=confidence interval; max=maximum; min=minimum; PVRI=pulmonary vascular resistance index; SD=standard deviation

The original unit "dyn sec m^2/cm^5" was converted to "Wood m^2" and analyzed. The 95% confidence interval of change from baseline is calculated from the mean and standard deviation.

In the macitentan 10 mg group, the geometric mean of fold change and its 95% confidence interval were 71.4% (62.5%, 81.6%). Given that the MM event was shown to be effective in the macitentan 10 mg group, it would be clinically meaningful if the point estimate of PVRI fold change (Week 24 to baseline) was equal to or less than 81.6%.

Pharmaceuticals and Medical Devices Agency (PMDA) published review report and application material for pediatric PAH patients with sildenafil. As a posthoc analysis, the results of the fold change in PVRI for sildenafil was described in the application material. The maximal oxygen uptake was defined as the primary endpoint in a pediatric global study of sildenafil (A1481131). The exploratory analysis was performed to investigate correlation between fold change in the maximal oxygen uptake and PVRI. The analysis results revealed that a 20% decrease of fold change in PVRI corresponds to the ≥10% fold change in exercise tolerance. Thus, a ≥20% decrease was defined as "improvement".

In macitentan 10 mg group of AC-055-302, equal to or less than 81.6% fold change can be interpreted as clinically meaningful fold change. This result in AC-055-302 of macitentan was consistent with the post-hoc analysis results in sildenafil.

Therefore, success criterion is defined as below:

$$geometric\ mean\ of\ fold\ change\ in\ PVRI\ at\ Week\ 24 \leq 81.6\%$$

Sample Size and Probability of Success

The primary endpoint is the fold change in PVRI at Week 24. It is assumed that treatment effect in the Japanese pediatric PAH patients is similar with that in the Japanese adult PAH patients. The treatment effect in the Japanese pediatric PAH patients was estimated based on the results from a clinical study (AC-055-307), conducted in Japanese adult PAH patients. The pediatric PAH patients are mainly consisted of idiopathic PAH, hereditary PAH, and congenital heart disease PAH who receive PAH medication. Using AC-055-307 study data, an analysis was performed on the subgroup who had idiopathic PAH, hereditary PAH, or congenital heart disease PAH (Table 4).

Table 4: PVRI Fold Change from Baseline to Week 24 (PPS/pseudo-pediatric population)- AC-055-307

	PP Set	Pseudo-pediatric
N	28	9
Geometric mean	60.6%	55.2%
[95%CI]	[52.5%, 70.1%]	[39.2%, 77.8%]

Abbreviations: CI=confidence interval; PPS=per protocol set; PVRI= pulmonary vascular resistance index.

It is assumed that the PVRI fold change at Week 24 follows log-normal distribution. The estimated mean and standard deviation were -0.594 and 0.4459, respectively, after the PVRI fold change converted to natural logarithm.

The success criterion for the study is defined as ≤81.6% of the geometric mean of fold change in PVRI at Week 24. The probability to achieve success criterion was calculated, assuming that the PVRI fold change is log-normally distributed.

The true PVRI fold change was assumed to be 60%, 70%, and 80%. Standard deviation of logarithmic PVRI fold change was assumed to be 0.40, 0.50, and 0.60. Based on these assumptions, probability to achieve success criterion was calculated with sample size ranging from 4 to 6 patients (Table 5).

Table 5: Sample Size and Probability of Success (%)

Assumption		Sample size		
True fold change	SD	4	5	6
60%	0.40	93.8	95.7	97.0
	0.50	89.1	91.5	93.4
	0.60	84.7	87.4	89.5
70%	0.40	77.8	80.4	82.6
	0.50	73.0	75.4	77.4
	0.60	69.5	71.6	73.4
80%	0.40	53.9	54.4	54.8
	0.50	53.2	53.5	53.9
	0.60	52.6	52.9	53.2

SD: standard deviation of logarithmic PVRI fold change

Assuming the true PVRI fold change at Week 24 is 70% and the standard deviation of logarithmic PVRI fold change is 0.50, 5 participants demonstrate 75.4% probability to achieve success criterion.

PVRI fold change at Week 24 can be calculated when both measurements, baseline and Week 24, are available. Considering potential discontinuation of one participant without PVRI assessment of Week 24 during the study, total 6 participants was defined as sample size of this study.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Efficacy Analysis Set	All participants who receive at least 1 dose of study intervention.
PK Analysis Set	All participants who have received at least 1 administration of macitentan and whose measured plasma or blood concentration after macitentan administration for pharmacokinetic analysis is available.
Safety Analysis Set	All participants who receive at least 1 dose of study intervention.

PK: pharmacokinetic

9.4. Statistical Analyses

The SAP for Foreign Health Authority interactions will be finalized prior to the first database lock (DBL) (see Section 9.5). The SAP for the submission in Japan will be finalized prior to second DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1. General Considerations

Efficacy endpoints will be summarized over time by descriptive statistics. Descriptive summary statistics, such as n, mean, standard deviation (SD), median, geometric mean, inter quantile range, minimum, and maximum for continuous variables, and counts and proportions for discrete variables will be used to summarize data. No statistical test will be performed due to the small sample size and insufficient statistical power. Unless otherwise specified, no imputation will be applied to the analysis. The efficacy endpoints will be analyzed using efficacy analysis set. The detailed methods of analysis and the data-handling rules will be provided in SAP.

The safety analysis set is used for the analyses of the safety variables. Adverse events, SAEs, related AEs, AEs by severity and treatment-emergent AEs will be summarized by system organ class (SOC) and preferred term (PT). Descriptive statistics would be provided for all other safety assessments (clinical laboratory parameters, vital signs and ECG parameters).

The PK analysis set will be used for the analyses of macitentan and aprocitentan concentrations.

Although there are 4 dosage defined by the body weight, participants will be analyzed as treated with macitentan (ie, analysis by dosage will not be applied, if not specified). In this study, a patient under 2 years old can be enrolled. However, it is not essential to enroll a patient under 2 years old. A patient under 2 years old will be included in the primary endpoint analysis when enrolled.

9.4.2. Primary Endpoint

Primary endpoint is the fold change in PVRI at Week 24. The geometric mean of PVRI fold change at Week 24 will be estimated with observed values. The success criterion is defined as the

geometric mean of PVRI fold change at Week 24 ≤ 81.6%. The success criterion will be evaluated using the calculated numerical geometric mean of PVRI fold change before rounding.

PVRI fold change at Week 24 is defined as below.

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

Estimand

The primary estimand is described according to the following 4 attributes:

1. Population: Participants between ≥ 3 months and < 15 years old with a diagnosis of PAH.
2. Variable: PVRI fold change at Week 24.
3. Intercurrent events: The following intercurrent events to be considered:

Intercurrent events	Strategy
Death	A while on treatment strategy will be used for deaths occurring up to 7 days after study intervention discontinuation. All assessments prior to the death will be considered in the analysis as observed.
Premature discontinuation (study intervention discontinuation/study participant discontinuation)	A while on treatment strategy will be used for premature discontinuation of study intervention. Premature discontinuation might occur due to the several reasons that are possibly treatment related (eg, clinical worsening, lack of efficacy, adverse events, informed consent withdrawal due to tolerability issues). Values after the premature discontinuation will be affected with these reasons and interpretation of the estimate will be of difficulty. All assessments prior to the premature discontinuation will be considered in the analysis as observed.
Administration of rescue therapy (initiation or change in PAH medication)	A while on treatment strategy will be used for administration of rescue therapy. All assessments after administration of rescue therapy will be ignored in the primary analysis. In the usual medical practice with infant/children in PAH, rescue therapy is easily added with the naïve patients comparing with the patients with PAH concomitant medications.

4. Population-level summary (estimator): Geometric mean of PVRI fold change at Week 24 with observed values prior to intercurrent events based on the efficacy analysis set.

Primary analysis

With efficacy analysis set, summary statistics and 95% confidence interval will be calculated with the PVRI fold change at Week 24. This study is considered as positive if the geometric mean of PVRI fold change at Week 24 is equal to or less than 81.6%. Thus, we will confirm the establishment of the following formula:

$$geometric\ mean\ of\ PVRI\ fold\ change\ at\ Week\ 24 \leq 81.6\ [\%]$$

The 95% confidence interval will be prepared only to show the precision of the fold change estimate and will not be used for the decision to declare the study as positive.

In the primary analysis, missing value will not be imputed. Only the observed value is used for the analysis.

9.4.3. Secondary Endpoints

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)
Biomarker	NT-proBNP
Echocardiography	Tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LVEI)
QOL	PedsQL™ 4.0 Generic Core Scales Short Form (SF-15)
Physical activity	Accelerometry

9.4.3.1. Hemodynamic Parameters/Right Heart Catheterization

The following pulmonary hemodynamic parameters will be measured by right heart catheterization: Summary statistics will be calculated for baseline measurements, measurements at Week 24, fold change, and change from baseline. For fold change, geometric mean and geometric CV% will be calculated. The definitions of change and fold change will be the same as those used for the analysis of PVRI. Time point: Baseline, Week 24. Pulmonary hemodynamic parameters: PVR (Wood), CO (L/min), mRAP (mmHg), mPAP (mmHg), SvO_2 (%), TPR (dyn sec/cm^5), CI (L/min/m^2).

9.4.3.2. WHO FC I or II (Yes/No)

The proportion of subjects having WHO FC I or II will be calculated at each timepoint of assessment. The proportion of subjects whose WHO FC value is categorized as I/II or III/IV will also be calculated at every timepoint.

9.4.3.3. Panama FC I or II (Yes/No)

The proportion of subjects having Panama FC I or II will be calculated at each timepoint of assessment.

9.4.3.4. 6-minute Walk Test

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.

9.4.3.5. Percent of Baseline in Plasma NT-proBNP

The percent of baseline in plasma NT-proBNP is defined as following formula:

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

9.4.3.6. Echocardiography Variables

The echocardiographic variables of interest are TAPSE and left ventricular eccentricity index expressed as change from baseline to Weeks 12, 24, and 52.

9.4.3.7. Quality of Life

The Pediatric Quality of Life Inventory™ (PedsQL™) questionnaire is used:

- PedsQL™ 4.0 SF-15 Short Form Generic Core Scales score

Expressed as change from Baseline to each post-baseline timepoint of assessments. The mean score for each scale is calculated according to the algorithm in the scoring manual (see Appendix 9: Quality of Life assessments). Where applicable the total score is used in calculation of the mean.

QoL variables will be analyzed separately depending on subjects or caregivers report.

9.4.3.8. Physical Activity (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.

Expressed as change from Baseline to Weeks 12, 24, and 52.

To be considered evaluable, physical activity should have been measured for at least 4 complete days at a specific timepoint of assessment. A complete day is defined as a record of at least 7 hours of data (after excluding the periods when the device was apparently not worn). These limitations allow for obtaining reliable results (Robertson 2011).

Secondary efficacy endpoints will be summarized over time by descriptive statistics. The detailed methods of analysis and the data-handling rules will be provided in the SAP.

9.4.4. Exploratory Endpoints

Exploratory endpoints (morbidity/mortality) are listed below:

- Time to morbidity/mortality
- Time to hospitalization or death due to PAH
- Time to hospitalization due to PAH
- Time to death due to PAH
- Time to death

The detailed methods of analysis and the data-handling rules for the exploratory endpoints will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent AEs will be summarized by SOC and PT. 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. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Adverse events of special interest (see Section 8.4.6) will also summarized by SOC and PT. More specification of other special interesting events will be defined in the SAP. A summary table will not be provided if the number of events is too few to provide meaningful summary.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for all laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided. Frequency tabulations of the laboratory abnormalities will be provided. Detailed specification of the laboratory abnormalities will be defined in the SAP.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QTcB and QTcF.

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves.

Vital Signs

Vital signs including pulse/heart rate, and blood pressure (systolic and diastolic) (supine, sitting or standing) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized. Abnormality criteria will be applied to baseline and postbaseline values. Incidence of vital signs abnormalities will be summarized. Definition of abnormality criteria will be provided in the SAP.

9.4.6. Pharmacokinetic Analyses

Unless otherwise specified, PK analyses will be based on the PK analysis set. Pharmacokinetic analysis will be performed by or under the responsibility of the sponsor.

All plasma or blood concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be used to summarize macitentan and aprocitentan plasma or blood concentrations at each sampling time point and PK parameters of macitentan and aprocitentan: AUC_{τ}, C_{max}, and t_{max}. Detailed rules for the analysis including exclusion from PK analyses will be specified in the SAP.

If deemed appropriate, the data from other studies of macitentan may be combined for the population analysis. If population analysis is performed, the detail and results will be provided in separate analysis plan and report. If sufficient data are available, population PK analysis of plasma or blood concentration-time data of macitentan and aprocitentan will be performed using nonlinear mixed effects modeling. If the population PK analysis is conducted, details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

9.5. Interim Analysis

This study plans 3 database locks (DBLs).

1. The first DBL will occur when 2 participants < 2 years of age have completed evaluations at Week 24. The dataset at first DBL will be used to support Foreign Health Authority interactions and will be summarized in a separate report.
2. The second DBL will occur at Week 24 when all participants complete evaluations at Week 24 and both PVRI measurements at baseline and at Week 24 are available with at least 5 participants. The dataset at second DBL will be used for the submission in Japan.
3. The third DBL will occur at the end of study when all participants complete evaluations at Week 52 and consecutive safety follow-up. The dataset at third DBL will be provided for the long-term safety evaluation during new drug application (NDA) review by PMDA. The SAP will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration time curve
AUC_{τ}	area under the concentration-time curve during one dosing interval
BP	blood pressure
CHD	congenital heart disease
CI	cardiac index
CL	confidence limits
C_{max}	maximum concentration
CO	cardiac output
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CTD	connective tissue disorder
CYP	cytochrome P450
DBL	database lock
dPAP	diastolic pulmonary artery pressures
dSAP	diastolic systemic arterial pressure
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EOS	end of study
EOT	end of treatment
ERA	endothelin receptor antagonist
ET	endothelin
EU	European Union
FC	functional class
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board
INR	international normalized ratio
IPPI	Investigational Product Procedure Instructions
IPPM	Investigational Product Procedure Manual
IRB	Institutional Review Board
IV	intravenous
LVEDP	left ventricular end diastolic pressure
LLN	lower limit of normal range
LOQ	limit of quantification
MM	morbidity/mortality
mPAP	mean pulmonary artery pressure
mRAP	mean right atrial pressure

NT-proBNP	N-terminal pro–brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PCC	protocol clarification communication
PD	pharmacodynamic
PDE-5	phosphodiesterase-5
PedsQL™	Pediatric Quality of Life Inventory™
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetic analysis
PPS	per-protocol set
PQC	product quality complaint
PRO	patient-reported outcome
PT	preferred term
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
QoL	quality of life
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RHC	right heart catheterization
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF	short form
SOC	system organ class
sPAP	systolic pulmonary artery pressures
sSAP	systolic systemic arterial pressure
SUSAR	suspected unexpected serious adverse reactions
SvO_2	mixed venous oxygen saturation
TAPSE	tricuspid annular plane systolic excursion
t_{max}	time to reach maximum concentration
TPR	total pulmonary resistance
ULN	upper limit of normal range
US	United States
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
WU	wood unit
β-hCG	β-human chorionic gonadotropin

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Blood urea nitrogen (BUN) Creatinine Creatinine clearance[c] eGFR	Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total and direct bilirubin Alkaline phosphatase Calcium
	Note: Details of liver chemistry stopping criteria and required actions and follow-up are provided in Section 7.1.3. Possible Hy's Law case (ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN) reporting requirements are defined in Section 8.4.6.	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
	If dipstick result is abnormal, or microscopy will be used to measure sediment. In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.	
Other Screening Tests	• Serum Pregnancy Testing (for women of childbearing potential only) at the time of screening and • Monthly Urine Pregnancy Testing for women of child bearing potential to be done at home under parental supervision	

[c] Creatinine Clearance (ml/min) =Males [[140-Age (years)] * Weight (kg)] / [72 * Serum Creat (mg/dl)]
Creatinine Clearance (ml/min) =Females [0.85* [140-Age (years)] * Weight (kg)] / [72 * Serum Creat (mg/dl)]

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Protocol Supplementary Information, which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the

situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process and Assent Form

Each participant (or a legally acceptable representative) must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort

participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent/assent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent/assent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent/assent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent/assent of the participant or legally acceptable representative is obtained.

Children (minors) or participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. Written assent should be obtained from participants who are able to write. A separate assent form written in language the participant can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the participant, and to the participant's parent(s) or if applicable legally acceptable representative.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate

technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

10.3.5. Committees Structure

An Independent Liver Safety Data Review Board (ILSDRB), a non-study specific external expert committee of hepatologists, will be established to review serious hepatic events. The ILSDRB will receive cases of serious hepatic events of special interest from the sponsor and provides ongoing assessment and advice regarding cases that may require further evaluation during the study.

10.3.6. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding macitentan or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of macitentan, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.7. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of ECG, possibly 6MWT data, as well as clinical laboratory data from a central

laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor may review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.8. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.9. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information/patient diary; and

date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

10.3.10. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.11. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.12. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.13. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.4.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

  *Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be

reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For macitentan, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention

- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for standard monitoring of a pre-existing disease or medical condition that did not worsen.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Protocol Supplementary Information, which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy. In addition, the following cases will be considered as permanent sterilization for this study: a premature ovarian failure confirmed by a specialist, a XY genotype, a Turner syndrome or participant born without a uterus.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly.
Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion/ligation
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Vasectomized partner
• Hormonal contraception
• Male condom with or without spermicide
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

10.6. Appendix 6: Sponsor Heart Catheterization Guidance

SPONSOR HEART CATHETERIZATION GUIDANCE WHEN HEMODYNAMIC VARIABLES ARE ENDPOINTS

- This guidance only applies to participants who will require a baseline and a post-baseline right heart catheterization (RHC) with/without a left heart catherization (LHC) (if needed). This guidance does not apply to RHC/LHC used only for participant eligibility.
- Hemodynamic evaluations will be carried out according to this guidance for those conditions and hemodynamic parameters that are described below. Further hemodynamic evaluations will be carried out according to the catheterization laboratory's local practice.

1. HEART CATHETERIZATION PROCEDURES

1.1 Conditions

Participants will undergo RHC/LHC at the study site (or other institution in case no suitable catheterization laboratory is available at the study site) in an appropriate care setting (eg, catheterization laboratory or medical procedures unit). If the assessment is performed at an external catheterization laboratory, the Primary Investigator is responsible to provide this guidance document to the external institution and to ensure that the catherization lab is sufficiently qualified.

Whenever possible, it is recommended that baseline and any post-baseline RHC/LHC are performed by the same operator, according to the same standards and procedures and in the same catheterization laboratory to ensure data consistency.

Where historical RHC/LHC is used for baseline measurements, then this guidance requirements for zeroing (Section 1.2) and heart catheterization measurement (Section 2) must have been followed and documented in the source notes. Otherwise a new RHC/LHC assessment will have to be performed for baseline measurements.

1.2 'Zeroing'

- 'Zeroing' must be done prior to any RHC/LHC measurements. The participant needs to be in a supine position and the pressure transducer is to be set to zero level at the mid-thoracic line.
- This must be documented in the heart catherization worksheet.

1.3 Oxygen

If the participant requires supplemental oxygen during baseline RHC/LHC, oxygen should also be given during the follow-up RHC/LHC, if needed.

2. HEART CATHETERIZATION MEASUREMENTS

2.1 Right Heart Catheterization measurements

- **Pulmonary Artery Pressure (PAP)**

  The participant will be asked to breath normally during the procedure. The operator will assess the appropriate systolic PAP (sPAP) and diastolic PAP (dPAP) readings based on the respiratory cycle and the pressure tracings.

  The sPAP and dPAP must be measured with 2 measurements documented in the source notes that are assessed by the operator as the most representative and reliable.

  If more than 2 values are recorded, all values must be documented on the source notes.

- **Pulmonary Artery Wedge Pressure (PAWP)**

  The participant will be asked to breath normally during the procedure. The operator will assess the appropriate pulmonary artery wedge pressure (PAWP) reading based on the respiratory cycle and the pressure tracing.

  If multiple measurements are performed, all PAWP values must be documented in the heart catherization worksheet.

  The operator must identify the most accurate PAWP on the heart catherization worksheet, based on their decision of which waveform to use.

- **Cardiac Output**

The same method for CO measurement must be used for both the baseline and any post-baseline RHC to ensure consistency.

If **thermodilution method** is used:

- The CO must be measured with at least 3 measurements documented in the heart catherization worksheet.
- The 3 measurements must be within 10% of each other, ie, the lowest of the 3 CO values must not be lower than 10% of the middle value AND the highest value must not be higher than 10% of the middle value.
- If the 3 values are not within 10% of each other (as per above), additional measurements can be performed until 3 measurements are obtained that are within 10% of each other.
- If more than 3 measurements are taken, the largest and/or smallest outlying values in the opinion of the operator should be discarded until at least 3 values are within 10% of each other
- If more than 3 values are recorded, all values must be documented in the heart catherization worksheet.

If **Fick method** (indirect or direct) is used:

- Only 1 value is required and must be documented in the source notes.
- If multiple values are performed, all CO values must be documented in the source notes. In addition, the operator must identify the most representative and reliable CO value.

2.2 Left Heart Catheterization Measurement

- **Left Ventricular end Diastolic Pressure (LVEDP)**
  - LVEDP is to be recorded only when PAWP is not available or not reliable.
  - The participant will be asked to breath normally during the procedure. The operator will assess the appropriate LVEDP reading based on the respiratory cycle and the pressure tracing.
  - If multiple measurements are performed, all LVEDP values must be documented in the heart catherization worksheet.
  - The operator must identify the most representative and reliable LVEDP value on the heart catherization worksheet.

2.3 Other Measurements

HR, RAP, dSAP, sSAP, SvO_2 are measured as per local practice.

3. DOCUMENTATION

3.1 Tracings

All relevant tracings are to be recorded and saved/printed for each pressure measurement and filed as the participants' source notes (electronic or paper).

3.2 Heart Catheterization Worksheet

It is mandatory to use the study heart catheterization worksheet to capture documentation of each RHC with/without LHC assessments newly performed for the purpose of the study and report relevant data in the eCRF, as indicated.

It is not mandatory to use the study heart catheterization worksheet for historical RHC/LHC assessments.

10.7. Appendix 7: WHO Functional Class

Class I Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

Class II Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

10.8. Appendix 8: Panama Functional Class for Pediatrics

For children aged 0–0.5 year

Class I Asymptomatic, growing and developing normally, no limitation of physical activity. Gains head control and increases body tone from 0 to 3 months, then rolls over and has no head lag. Sitting with support.

Class II Slight limitation of physical activity, unduly dyspnoeic and fatigued. Falling behind physical developmental milestones. Comfortable at rest. Continues to grow along own centiles.

Class IIIa Marked limitation of physical activity, unduly fatigued. Regression of learned physical activities. Quiet and needs frequent naps. Comfortable at rest. Less than ordinary activity causes undue fatigue or syncope and/or presyncope. Growth compromised. Poor appetite. Requires excessive medical attention.

Class IIIb Growth severely compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue or syncope. Plus features of Class IIIa.

Class IV Unable to carry out any physical activity without undue dyspnea, fatigue or syncope, not interacting with family. Syncope and/or right heart failure. Plus features of Class III.

For children aged 0.5–1 year

Class I Asymptomatic, growing along own centiles, no limitation of physical activity. Mobile, sitting, grasping, starting to stand, crawling, playing.

Class II Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing. Delayed physical development. Comfortable at rest. Continues to grow along own centiles.

Class IIIa Marked limitation of physical activity. Regression of learned physical activities. Stops crawling. Quiet and needs frequent naps. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity causes undue fatigue or syncope and/or presyncope. Growth compromised. Poor appetite. Requires excessive medical attention.

Class IIIb Growth severely compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue or syncope. Plus features of Class IIIa.

Class IV Unable to carry out any physical activity without undue dyspnea, fatigue or syncope, not interacting with family. Syncope and/or right heart failure. Plus features of Class III.

For children aged 1–2 years

Class I Asymptomatic, growing along own centiles, no limitation of physical activity. Standing, starting to walk/walking, climbing.

Class II Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing. Delayed physical development. Comfortable at rest. Continues to grow along own centiles.

Class IIIa Marked limitation of physical activity. Regression of learned physical activities. Reluctant to play. Quiet and needs frequent naps. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity causes undue dyspnea, fatigue or syncope and/or presyncope. Growth compromised. Poor appetite.

Class IIIb Growth severely compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue or syncope. Plus features of Class IIIa.

Class IV Unable to carry out any physical activity without undue dyspnea, fatigue or syncope, not interacting with family. Syncope and/or right heart failure. Plus features of Class III.

For children aged 2–5 years

Class I Asymptomatic, growing normally, attending nursery/school regularly, no limitation of physical activity, playing sports with his/her classmates.

Class II Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing with his/her classmates. Comfortable at rest. Continues to grow along own centiles. Nursery/school attendance 75% normal. No chest pain.

Class IIIa Marked limitation of physical activity. Regression of learned physical activities. Not climbing stairs, reluctant to play with friends. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity (eg, dressing) causes undue dyspnea, fatigue, syncope and/or presyncope or chest pain. Nursery/schooling compromised < 50% normal attendance.

Class IIIb Unable to attend nursery/school, but mobile at home. Wheelchair needed outside home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue, syncope or chest pain. Plus features of Class IIIa.

Class IV Unable to carry out any physical activity without undue dyspnea, fatigue, syncope, or chest pain, unable to attend school, wheelchair dependent, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III.

For children aged 5–16 years

Class I Asymptomatic, growing along own centiles, attending school regularly, no limitation of physical activity, playing sports with his/her classmates.

Class II Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing with his/her classmates. Comfortable at rest. Continues to grow along own centiles. School attendance 75% normal. No chest pain.

Class IIIa Marked limitation of physical activity. No attempt at sports. Comfortable at rest. Less than ordinary activity causes undue dyspnea, fatigue, syncope or chest pain. Schooling compromised < 50% normal attendance.

Class IIIb Unable to attend school, but mobile at home and interacting with friends. Wheelchair needed outside the home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity (eg, dressing) causes undue dyspnea, fatigue, syncope and/or presyncope or chest pain. Plus features of Class IIIa.

Class IV Unable to carry out any physical activity without undue dyspnea, fatigue, syncope, or chest pain, unable to attend school, wheelchair dependent, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III.

10.9. Appendix 9: Quality of Life assessments

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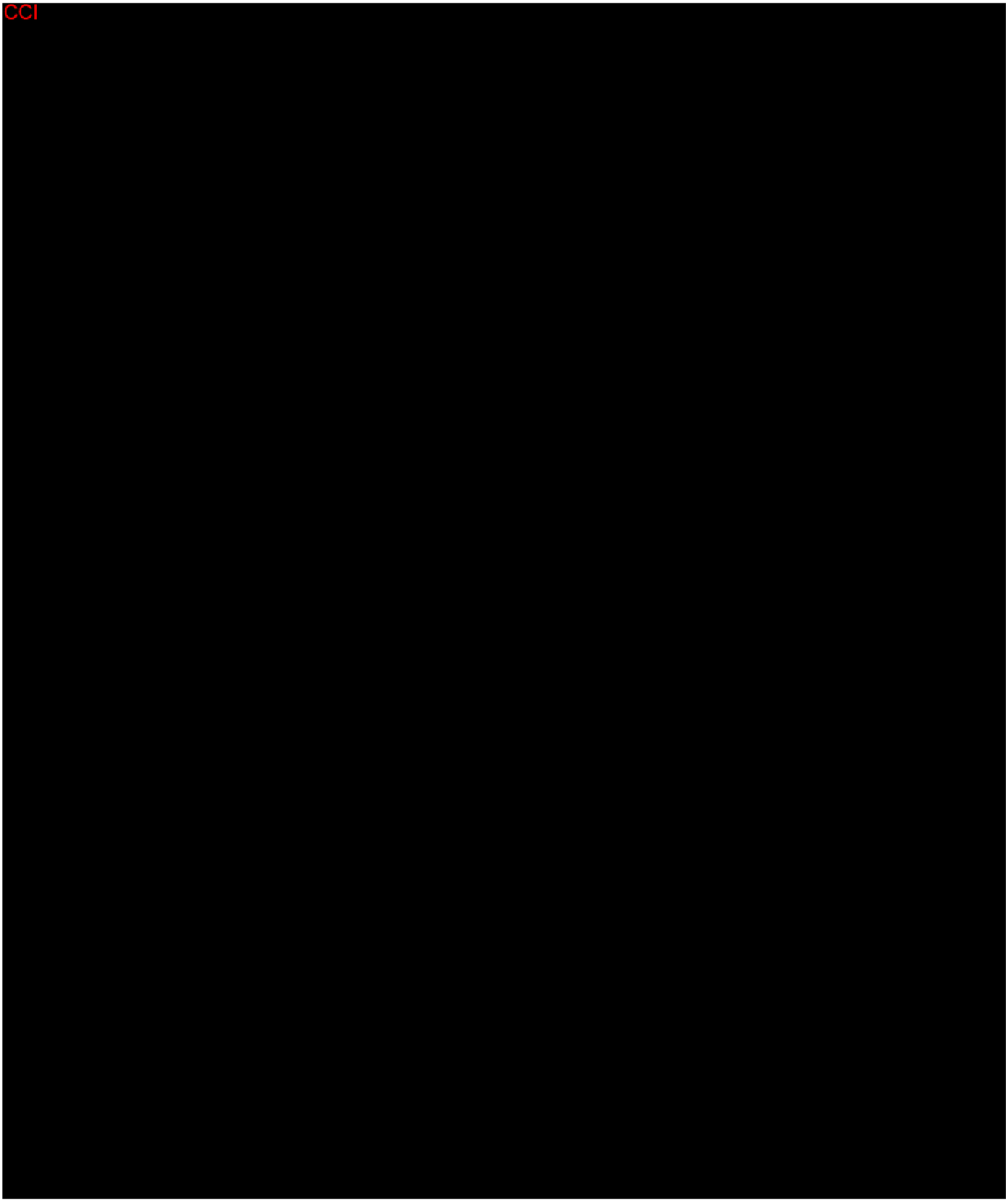

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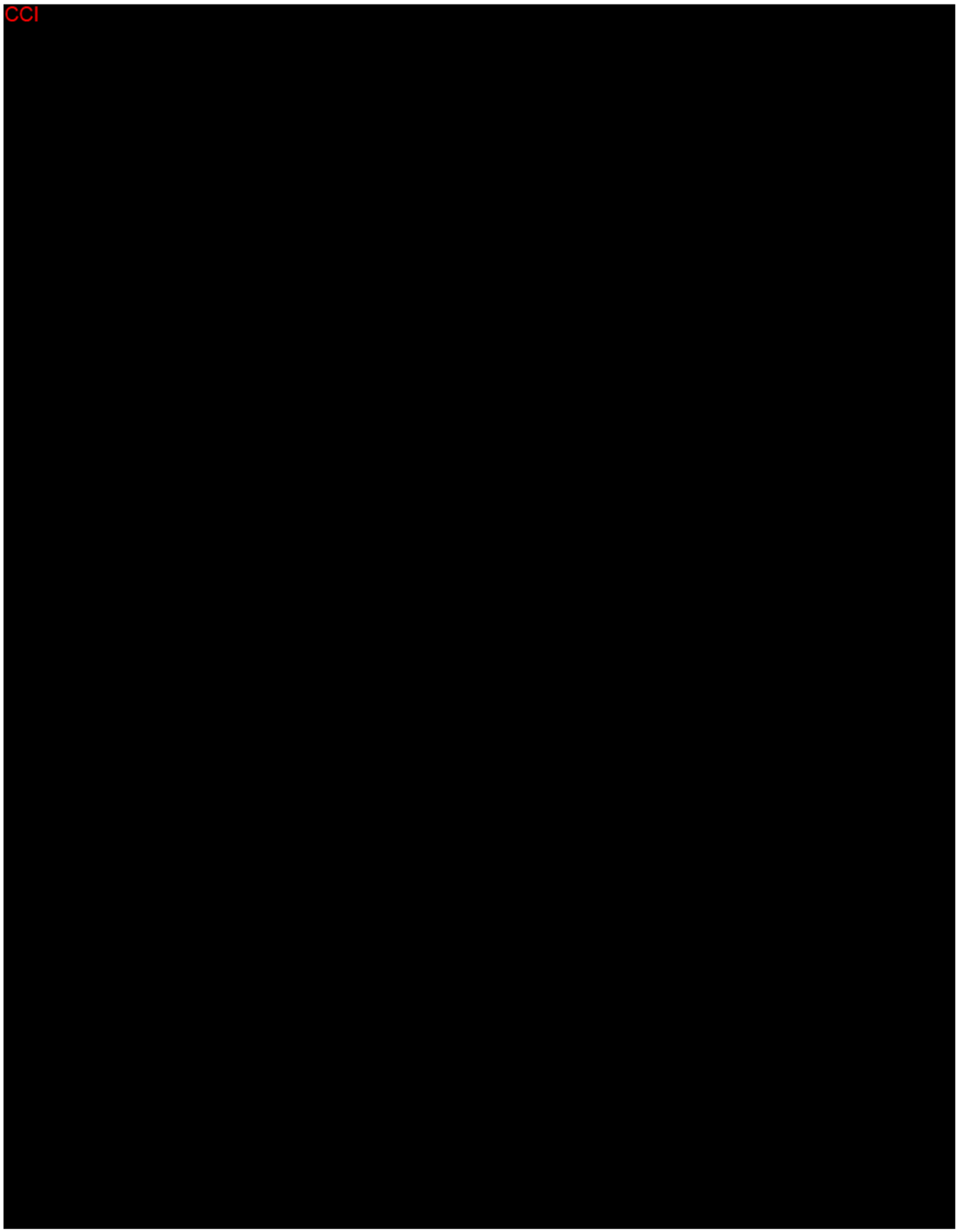

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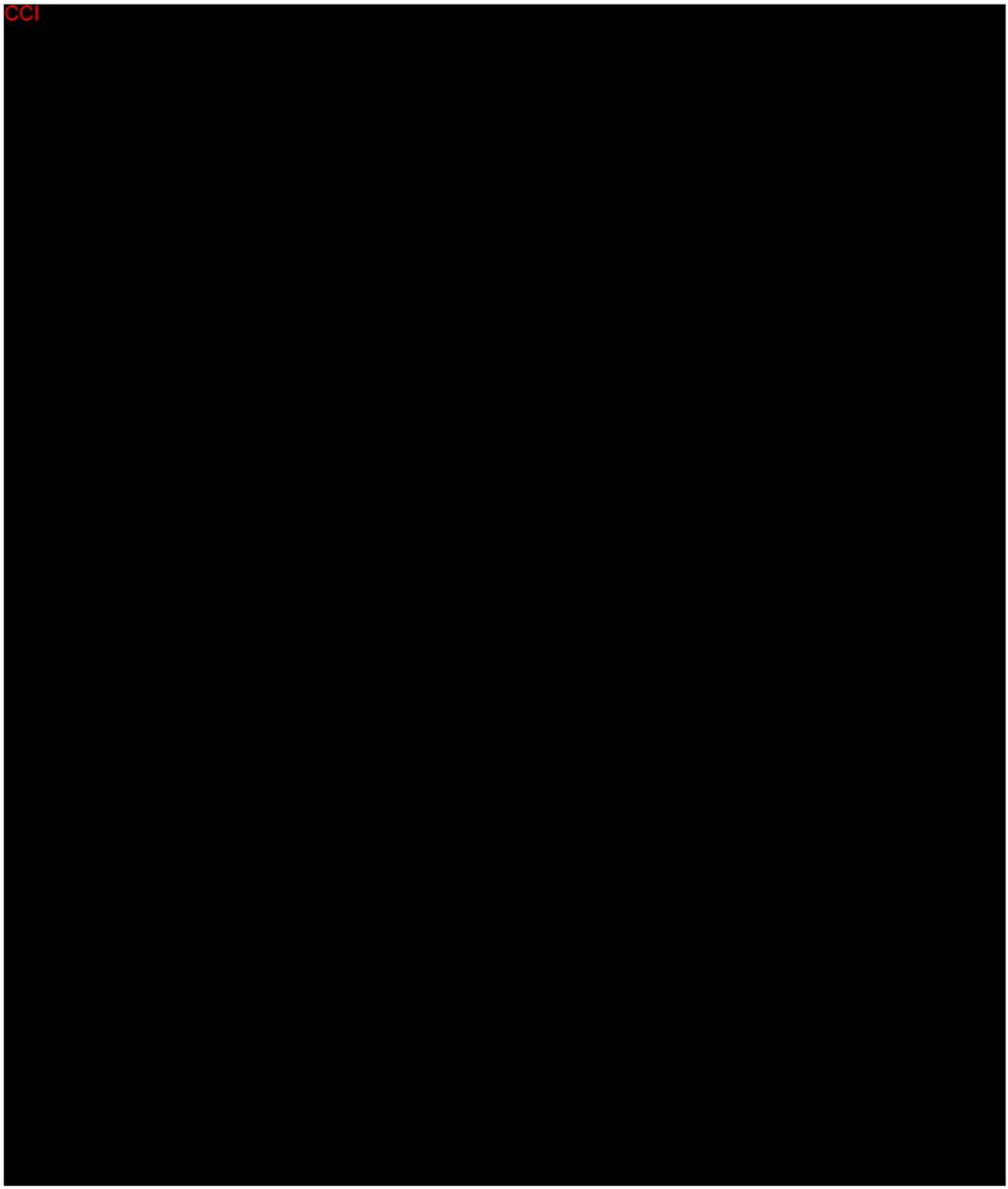

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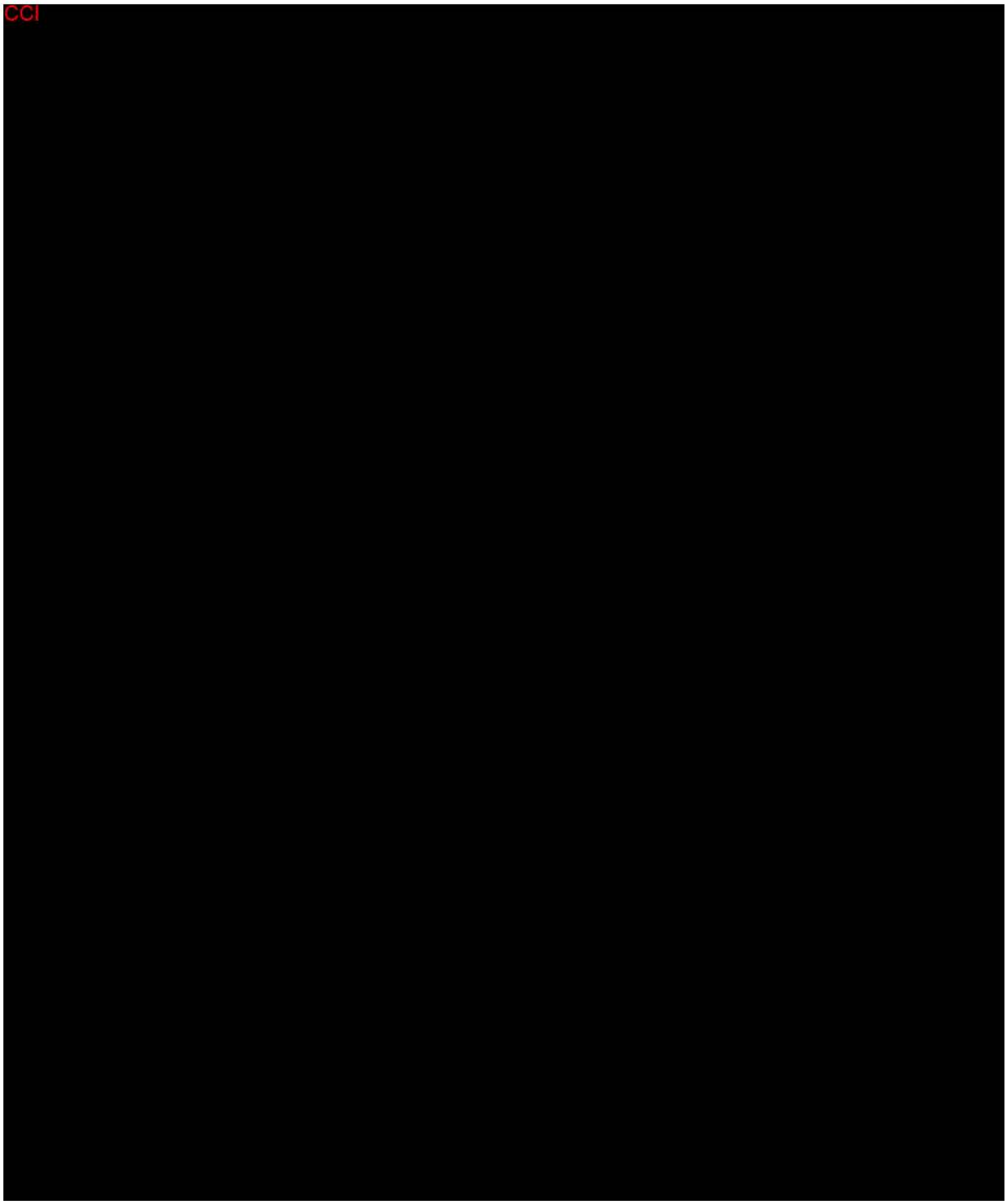

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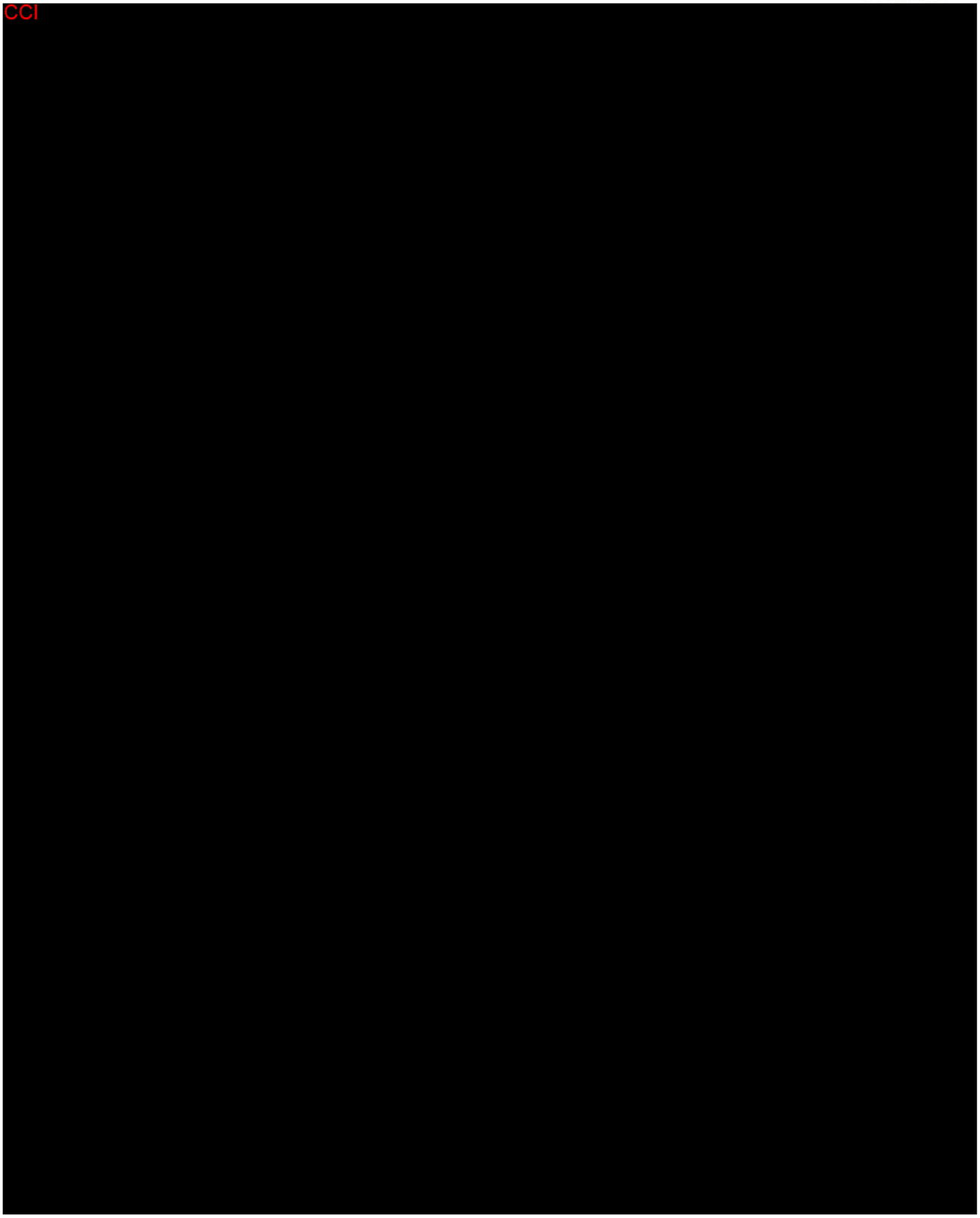

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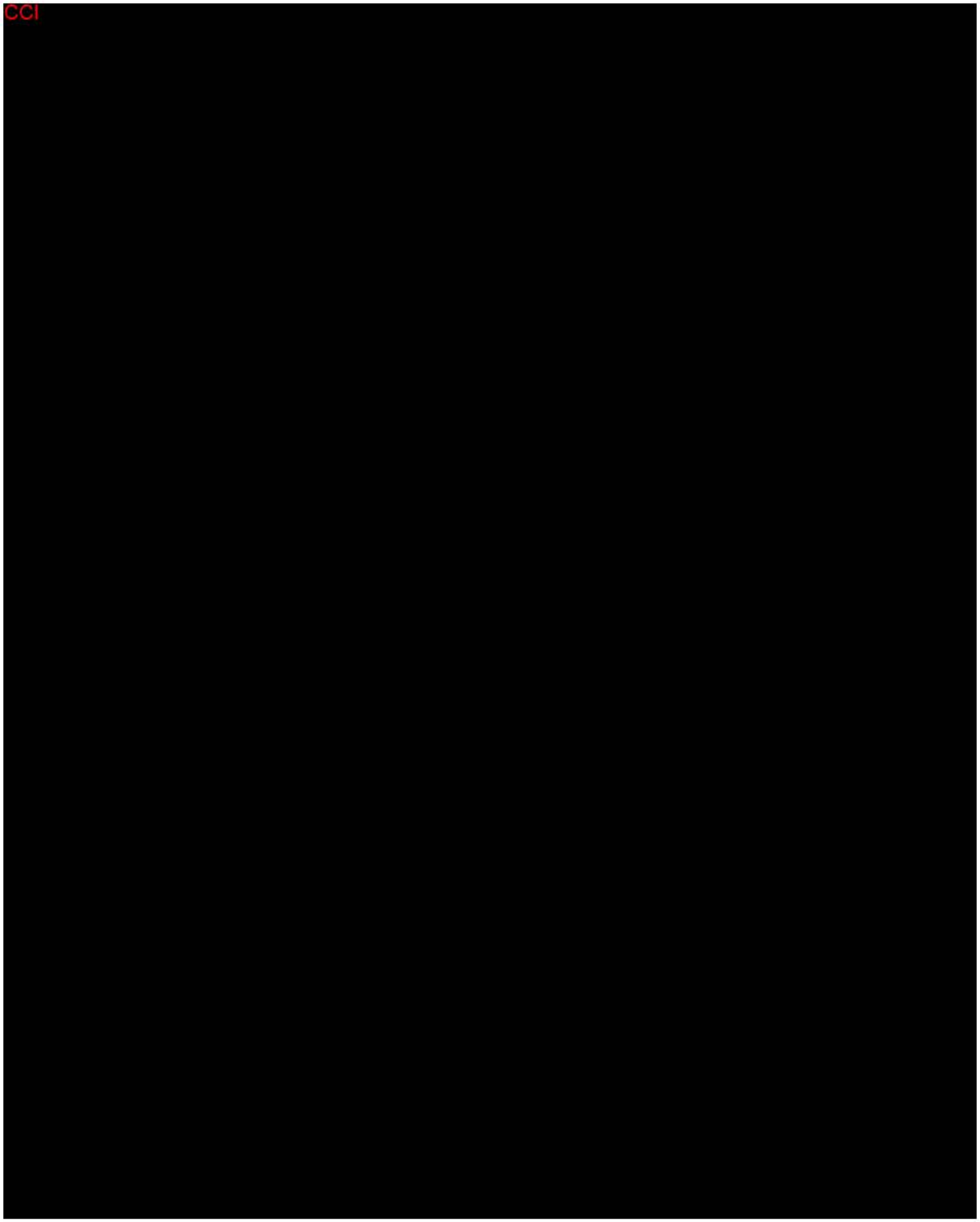

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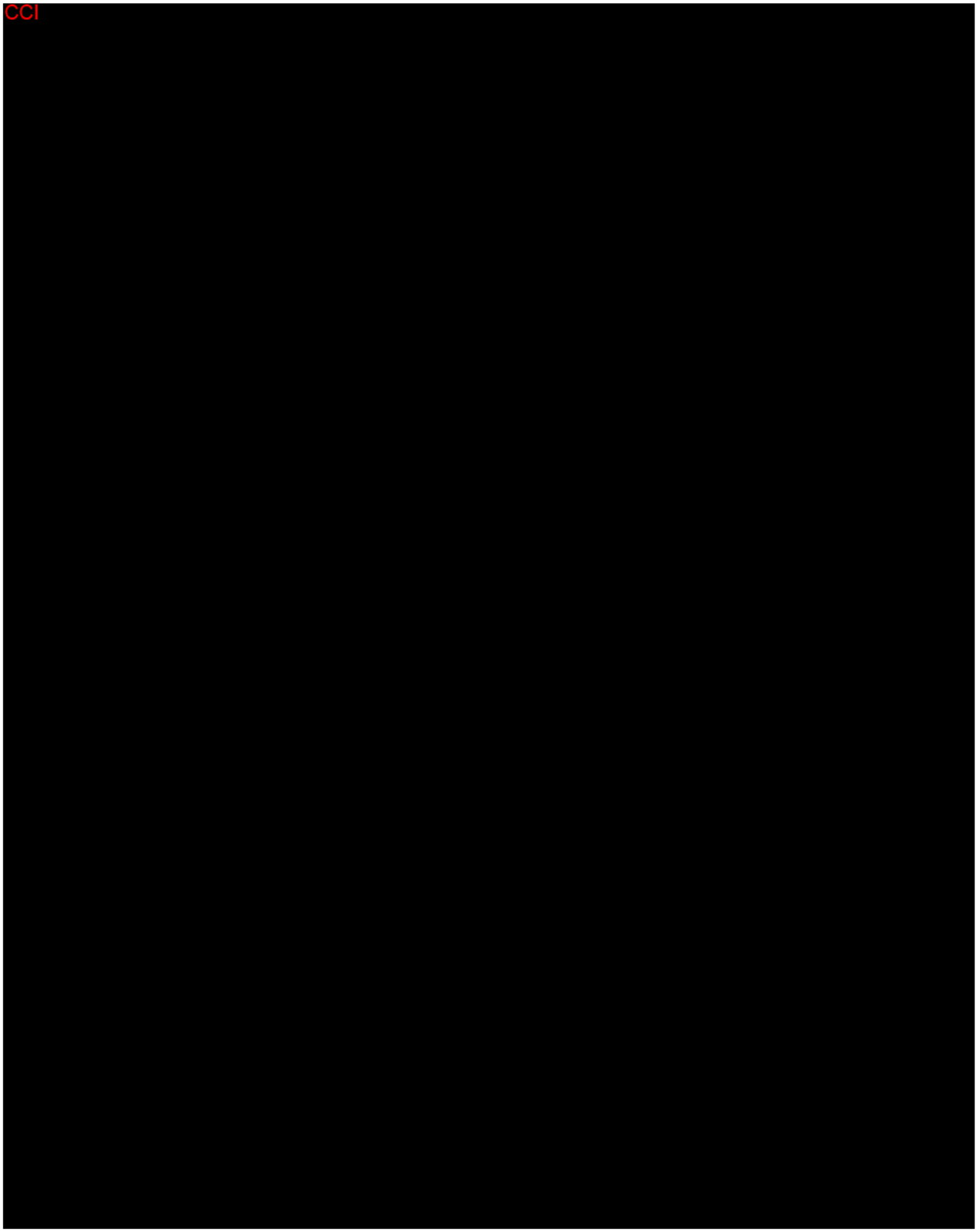

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10.10. Appendix 10: Sponsor 6-minute Walk Test Guidance

This document stipulates the criteria under which study-required 6MWTs will be carried out in Clinical Protocol 67896062PAH3001.

These criteria are, in part, derived from the recommendations included in the American Thoracic Society (ATS) Guidelines issued in 2002 and the ERS/ ATS Technical Standard published in 2014 (ATS Statement 2002). As opposed to the comprehensive published manuscripts, this guidance has been shortened and accustomed for use in a clinical study in which a variety of different assessments may need to be performed at a given visit.

1. INSTRUCTIONS

General

- The 6-Minute Walk Test (6MWT) must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track length for the 6MWT must be free of obstacles. The use of treadmill and a continuous course, eg, a circuit, is not allowed.
- The ideal track length used for the 6MWT is 30 meters (If the track is shorter, it must be no shorter than 20 meters in length). The track must be marked at regular intervals to facilitate measurement of the distance walked (markings every 3 meters are recommended). The turnaround points must be marked with a cone. A starting line, which marks the beginning and the end of each lap (one lap is twice the length of the track used at the site), needs to be marked on the floor.
- Local safety practice regarding medical emergencies and contraindications for 6MWT must be followed at each participating site.
- The person administering the 6MWT (tester) needs to stand near the starting line during the 6MWT and must not walk with the participant, and not get distracted during the conduct of this 6MWT (eg, by talking to someone).
- Rest periods are allowed if the participant can no longer continue. If the participant needs to rest, he/she may pause, lean against the wall and continue walking whenever he/she feels able. The timer must continue to run even if the participant stops to rest. The 6MWT can be stopped at any moment as due to medical emergencies or safety issues such as chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance
- The 6MWT is a non-encouraged test. An even tone of voice must be used when using the standard phrases. No other instructions or words of encouragement are given during the test, other than the pre-scripted phrases (see instructions to participant). Eye contact and body language signaling the participant to speed up must be avoided during the test.
- Whenever possible, for an individual participant, repeat 6MWTs must be conducted in the same corridor and by the same tester, and preferably at about the same time of the day (ie, within ± 2 hours of the baseline test) to minimize variability.
- If a participant is oxygen dependent, the flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT.

Additionally, the way oxygen is delivered (delivery device, application route, way of carrying delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.

Training tests

For participants who have not previously performed a 6MWT, a training 6MWT must be performed before the first protocol-mandated 6MWT is performed.

Data from the training 6MWT are not collected in the eCRF but must be documented in the source data.

Timing

Only two 6MWTs can be performed on the same day. The interval between two 6MWTs on the same day must be at least 2 hours.

2. TEST REQUIREMENTS

Participant

- The participant must wear comfortable clothing and appropriate walking shoes.
- The participant must not have exercised vigorously within 2 hours of beginning the test.
- It is recommended that the participant rests for at least 15 minutes before the test starts.
- It is recommended that participants receive their concomitant therapy on the day of the test. If the participant is used to taking bronchodilators, he/she must take them at least 10 to 30 min before the test.
- Participants can use their usual walking aids during the test (eg, cane). The same walking aid should be used for all 6MWTs. Walkers are not allowed.

Equipment to perform the test

- Countdown timer
- Mechanical lap counter
- Two cones to mark the turnaround points
- A chair that can be easily moved along the track
- 6MWT Worksheet
- Borg category-ratio (CR) 10 scale®

3. PERFORMING THE 6MWT

Assessments before the 6MWT

Before the 6MWT, the tester shows the Borg CR10 Scale® to the participant and asks the participant:

- *"Please grade your dyspnea using this scale".*

Record the baseline-6MWT dyspnea using the Borg CR10 scale® on the 6MWT worksheet.

Instructions to the participant during the 6MWT

The tester uses the following exact dialogue with the participant:

"The objective of this test is to walk as far as possible in 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation".

(The tester demonstrates the walking and pivots around a cone briskly).

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember the object is to walk AS FAR AS POSSIBLE in 6 minutes, but don't run or jog."

After these instructions are given to the participant, the tester says:

"Start now, or whenever you are ready"

As soon as the participant starts to walk, the tester starts the timer and writes down start time. The tester reminds the participant of the elapsed time by saying:

After the first minute: *"You are doing well. You have 5 minutes to go".*

When the timer shows 4 minutes remaining: *"Keep up the good work. You have 4 minutes to go."*

When the timer shows 3 minutes remaining: *"You are doing well. You are halfway done."*

When the timer shows 2 minutes remaining: *"Keep up the good work. You have 2 minutes to go."*

When the timer shows only 1 minute remaining: *"You are doing well. You have only 1 minute to go."*

If the participant stops walking during the test and needs a rest, the tester says:

"You can lean against the wall if you *would like; then continue walking whenever you feel able."*

The tester will not stop the timer. If the participant stops before the 6 minutes are up and refuses to continue (or the tester decides that they should not continue), the tester wheels the chair over for the participant to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, the tester says:

"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you".

When the timer alarm rings the tester says:

"Stop!"

Assessments after the 6MWT

The tester walks over to the participant, marks the spot where the participant stopped, records the total distance walked in the 6MWT worksheet and congratulates the participant on good effort.

After the 6MWT, the tester reminds the participant of their dyspnea that they chose before the 6MWT. The tester shows the Borg CR10 Scale® to the participant and asks the participant:

- *"Please grade your dyspnea using this scale".*

The tester will record the post-6MWT dyspnea on the 6MWT worksheet.

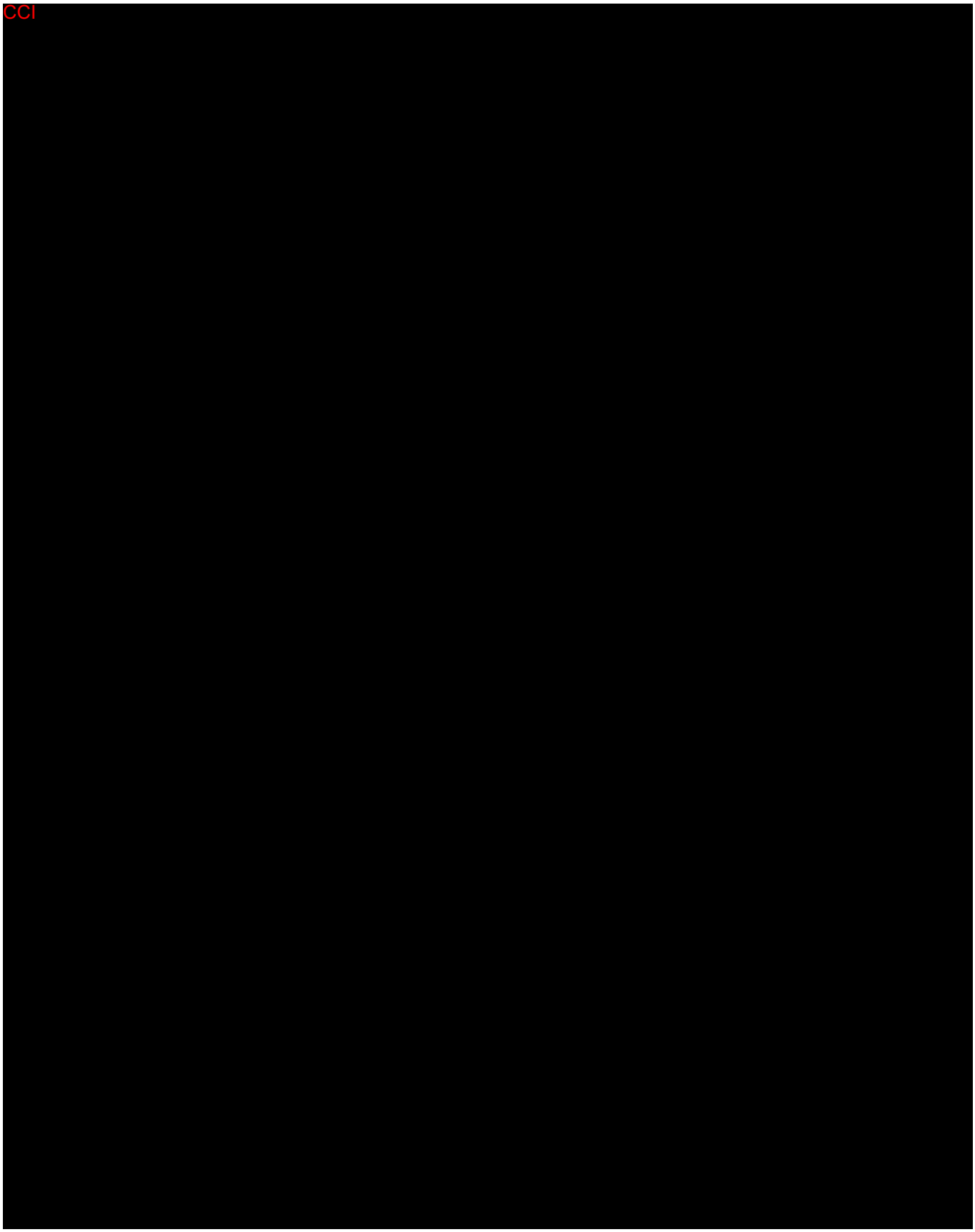
4. 6MWT WORKSHEET

It is mandatory to use the 6MWT worksheet to capture documentation of each 6MWT newly performed for the purpose of the study and report relevant data in the eCRF, as indicated.

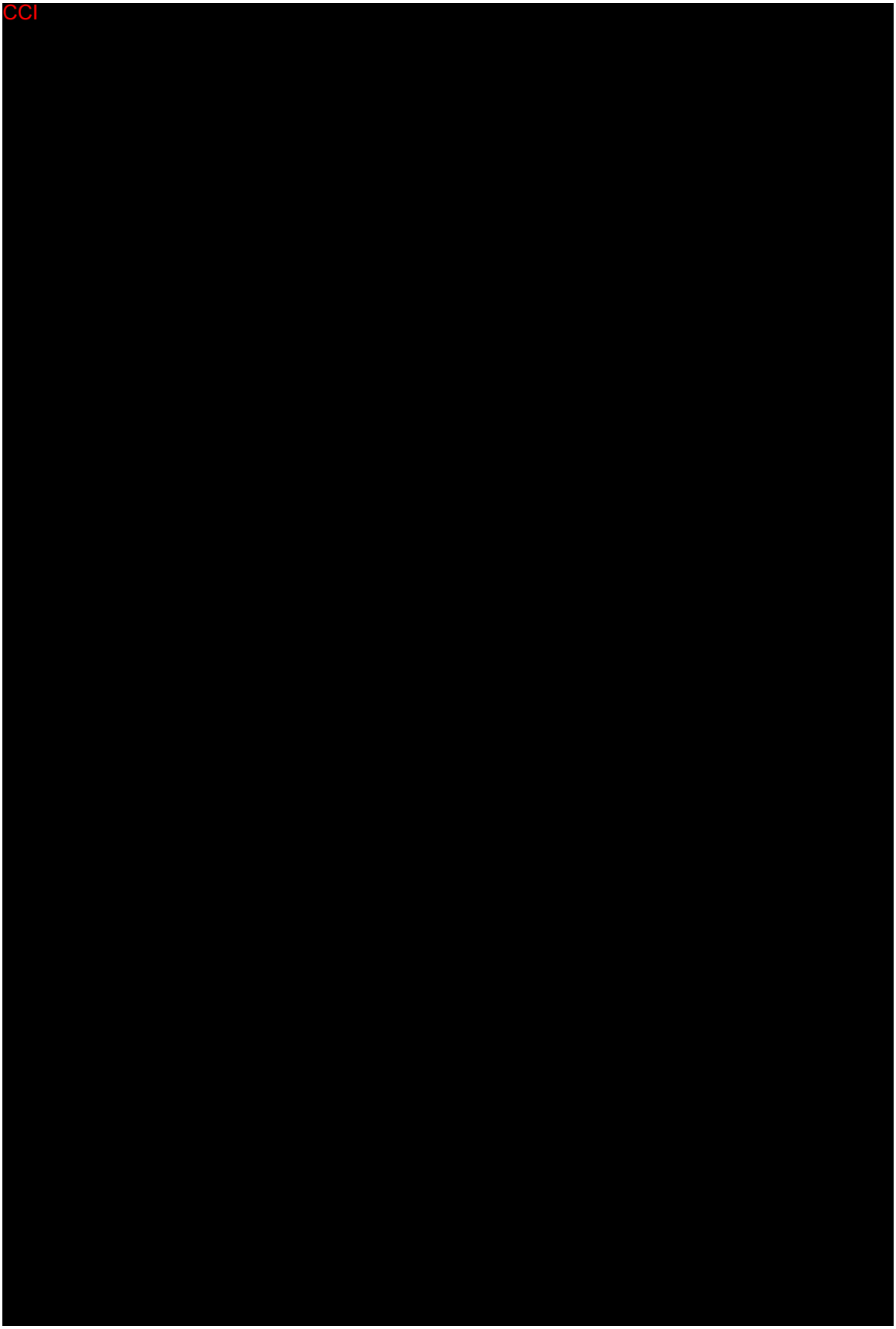
It is not mandatory to use the study 6MWT worksheet for historical 6MWTs.

10.11. Appendix 11: Borg CR10 Scale®

CCI



Borg CR10 Scale®:



10.12. Appendix 12: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING CORONAVIRUS DISEASE 2019

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted using the examples contained in this appendix, after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

If the participant has tested positive for the COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing. study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

STUDY VISITS

- Missed visits, missed assessments or assessments performed out of window due to COVID-19 will be captured in the clinical trial management system for protocol deviations with the prefix "COVID-19-related", with the actual visit date documented or reason for withdrawal specified. Other relevant study elements impacted by the pandemic should also be documented/labeled as "COVID-19 related" in the clinical trial management system for protocol deviations or other study system, as applicable.
- Discontinuations of study interventions and withdrawal from the study due to COVID-19 will be captured with the prefix "COVID-19-related" in the eCRF.
- Participants entering in screening who are not able to complete all screening assessments on site due to COVID-19 restrictions (eg, no on-site visit possible) would be considered screening failures.
- Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible by remote/virtually/home visits. This applies to all visits except Visit 1/Screening which must be conducted in person at the study site.

  For scheduled visits that cannot be conducted on-site options may include (as local regulations permit):

  - Involvement of a local registered nurse, or any other properly trained person, site study nurse or the participant's physician to collect required blood samples and/or perform physical examinations, as indicated per protocol (see Section 1.3 Schedule of Activities of the Protocol) for planned remote visits.
  - Blood sampling with central laboratory kits may be performed locally and shipped to the central laboratory. Alternatively, a local laboratory may be considered, in case the central laboratory kits cannot be used for the scheduled blood tests.
  - Telephone calls at scheduled visits or monthly at a minimum, if the window for scheduled visits is wider, with participant and their primary care physician, local nurse, etc if applicable.
  - Telemedicine consultation, if permitted by local regulation and if part of the local clinical practice.
  - Review of any available medical records.

Details regarding these contacts (date, time, contact person) must be properly documented in source records including a detailed content of the discussion points (eg, responses from participants and/or results of physical evaluation performed by the trained person or treating physician).

Participants will be asked to return to the site as soon as possible once restrictions are lifted to perform all assessments that would have been missed.

LABORATORY ASSESSMENTS

- For participants not able to perform their regular on-site scheduled visits due to COVID-19 pandemic (eg, due to self-isolation/quarantine, travel restrictions, limited access to hospitals, …), at least the planned safety assessments must be performed remotely, including safety laboratory assessments (eg, hematology, liver function test, and urine pregnancy test for women of childbearing potential) and physical examination.
- The investigator must review all safety assessments to confirm the participant can pursue his/her study intervention. If the safety assessments cannot be performed and reviewed by the investigator in a timely manner, the investigator may decide to interrupt or discontinue permanently study intervention, if it is in the best interest of the participant.

TREATMENT

- If the participant cannot come to the site for his visits, his/her study intervention may be provided, via direct-to-participant shipment, to the participant's home or a participant's relative/caregiver may pick up study drug on behalf of the participant, in accordance with local regulations.
- The participant will be asked to save and return unused tablets (study drug) at their next on-site visit. Treatment compliance will meanwhile be assessed via monthly phone calls.
- This distribution and shipment of study intervention will be done if the treating physician can ensure that they can maintain participant safety oversight (based on clinical evaluation, results of laboratory tests and pregnancy test, if applicable).

HANDLING OF SAFETY AND EFFICACY DATA INTEGRITY

The sponsor will monitor the COVID-19 related protocol deviations and evaluate their impact on study safety and efficacy outcomes.

The statistical analysis plan will specify details on addressing impact of COVID-19 related aspects on the analyses. This includes the following planned analyses (not limited to):

- Sensitivity analyses for primary and secondary efficacy endpoints to address intercurrent events caused by COVID-19, as well as handling of missing values caused by the limits from the COVID-19 pandemic.
- Summary of safety analyses (eg, AEs, SAEs) by COVID-19 (yes or no).
- Summary/listings of protocol deviations related to COVID-19.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 4 (9 March 2023)

Overall Rationale for the Amendment: The main reason for this protocol amendment is to add allowance for Day1 and to add interpretation of exclusion criteria, and to also allow for the use of local laboratory data for eligibility assessment. Minor corrections and editorial revisions are also being implemented.

The updates are indicated in bold for new text and strike-through for deleted text in the following table.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis 3. OBJECTIVES AND ENDPOINTS 8.2.7. Borg CR10 Scale®	The following words were corrected: Dyspnea ~~and~~ **on** exertion	For clarity and consistency
1.3. Schedule of Activities (SoA) ECG, Hematology, chemistry	Added allowance in footnote for Day 1: ECG **n. If there is no change in clinical conditions, data available within 14 days prior to Day1. Not required on Day 1 if screening assessment is performed within 14 days prior to Day1.** Hematology, chemistry **o. If there is no change in clinical conditions, data available within 7 days prior to Day1. Not required on Day 1 if screening assessment is performed within 7 days prior to Day1.**	To avoid short term invasive tests or restraint for exam, Day 1 assessments are not required if screening assessments are close to Day1
5.2. Exclusion Criteria	Criterion 15 is modified as follows: Previous treatment***** with macitentan at any time. ***It is not considered treatment if it does not affect the evaluation of efficacy and safety of this study. In such cases (eg, medical history of short-term macitentan administration), the investigator must contact the sponsor's responsible medical officer to confirm the interpretation is applicable.**	To clarify that the sponsor should be consulted to avoid discrepancies in the interpretation of ' treatment '.
6.8. Concomitant Therapy	The following sentence is added: **Non-therapeutic medications (Drug solution and heparin used for PK blood sampling or right heart catheterization, etc.) do not need to be recorded in the eCRF.**	For clarity and consistency. The purpose is to collect treatments that may affect the evaluation of efficacy and safety of macitentan.
8.2.2.2. Functional Class	The following sentence is deleted: ~~The disease progression event (ie, worsening of clinical condition related to PAH) must be reported in the eCRF within 24 hours of the investigator's knowledge of the event.~~ If the disease progression fulfills the seriousness criteria (eg,	For clarity and consistency

Section number and Name	Description of Change	Brief Rationale
	needs hospitalization), the event must also be reported as an SAE within 24 hours of the investigator's knowledge that the event is serious using an SAE reporting form.	
8.3.1. Physical Examinations	The following sentence is deleted: Weight and height of the participants will be measured at each visits until the end of the treatment ~~except for Visit 3 where only weight will be measured.~~	For clarity and consistency
8.3.4. Clinical Safety Laboratory Assessments	The following sentence is added: A central laboratory will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. **If the results from the central laboratory are not available in time for enrollment of the participant, the results from the local laboratory may be used for eligibility verification. The results with the corresponding normal ranges must be recorded in the eCRF.**	Conditions for use of local laboratory results at enrollment are clarified.
10.10. Appendix 10: Sponsor 6-minute Walk Test Guidance 10.11. Appendix 11: Borg CR10 Scale®	Deletion of description about exertion.	For clarity and consistency
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (9 March 2022)

Overall Rationale for the Amendment: The main reason for this protocol amendment is to change the inclusion/exclusion criteria, to update the method of administration and to modify the definition prohibited concomitant therapy. Minor corrections and editorial revisions are also being implemented.

The updates are indicated in bold for new text and strike-through for deleted text in the following table.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis Description of Interventions 6.1. Study Intervention Administered	The sentence is changed as follows: Whole tablet(s) are dispersed in water and administered orally **(eg, via spoon, glass, syringe)**. **The same administration method should be used as far as possible.**	To update information based on dispersible tablet formulation (not limited to spoons)
1.1. Synopsis SAFETY EVALUATIONS 1.3. Schedule of Activities (SoA) 10.2. Appendix 2: Clinical Laboratory Tests	The following items are deleted ~~Serology (hepatitis B surface antigen [HBsAg] and hepatitis C virus antibody)~~	To align with exclusion criteria
1.3. Schedule of Activities (SoA) Weight and height	Removed "weight only" and added "**X**"	For clarity and consistency (height is required to

Section number and Name	Description of Change	Brief Rationale
		assess eGFR)
1.3. Schedule of Activities (SoA) Pregnancy test	Added "**urine**" at Visit 12 and FU.	For clarity and consistency
1.3. Schedule of Activities (SoA) Echocardiography (TAPSE, LVEI)	Added allowance in footnote for Day 1: **l. Data available within 14 days prior to Day 1**	For clarity and consistency
1.3. Schedule of Activities (SoA) Visit 3	The following sentence is added in footnote k: k. Visit 3 will take place at steady-state conditions for macitentan and its active metabolite (aprocitentan), ie, patients must have received at least 10 days of continuous administration of the same dose of macitentan **(patients should take at the same dose level and time of day for 11 days prior to Visit 3 including the day of visit). After completion of the 24-hour PK collection, macitentan treatment will begin at the dose determined at Visit 3.**	Specification of points to be complied with in administration before PK measurement
5.1. Inclusion Criteria	Criterion 7 is modified the following: b. Of childbearing potential and o Practicing a highly effective, **preferably** user-independent method of contraception… Criteria 9, 10 and 11 were deleted.	To align with latest JNJ risk language (Clarified contraception requirements for pediatric study) Contraception is not required for male participant
5.2. Exclusion Criteria	Patients diagnosed with bronchopulmonary dysplasia were added to exclusion criterion 5. Criterion 23 was deleted. Criterion 28 was deleted. Added subtitles "Pulmonary hypertension related" and "Comorbidities related" to medical condition	To ensure that the infants entering in current study are not premature. Contraception is not required for male participant. This is a criterion for administration of immunosuppressants and is not appropriate for this study. For clarity and consistency
6.1. Study Intervention Administered	The following sentence is added: **The method of administration (eg, spoon) must be recorded in the eCRF.**	To update information based on dispersible tablet formulation (not limited to spoons).
6.8. Concomitant Therapy Prohibited Concomitant Therapy	The following sentence is added in strong inducers of CYP3A4 section: **If they cannot be avoided, their administration should be delayed to after the visits where PK samples are collected and limited to not more than 4 consecutive weeks.**	To allow continued administration of macitentan in the presence of strong CYP3A4 inducers but to avoid affecting

<table>
<tr><th>Section number and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td></td><td>PK measurements</td></tr>
<tr><td>6.8. Concomitant Therapy
Prohibited Concomitant Therapy</td><td>The sentence is changed as follows:
The administration of ERAs and/or of any investigational drug after the first administration of study intervention must lead to permanent discontinuation of macitentan. The ~~administration of any strong CYP3A4 inducer and/or any~~ systemic administration of a strong CYP3A4 inhibitor as well as administration of moderate dual CYP3A4/ CYP2C9 inhibitor or a combination of a moderate CYP3A4 and moderate CYP2C9 inhibitor must lead to interruption of macitentan</td><td>To clarify the action to be taken when any investigational drug is administered.
To allow continued administration of macitentan in the presence of strong CYP3A4 inducers since low exposure to macitentan is better than no exposure.</td></tr>
<tr><td>7.1.1 Permanent Discontinuation</td><td>The sentence is changed as follows:
If a participant initiates treatment with ERAs and/or of any investigational drug</td><td>For consistency with the prohibited concomitant therapy</td></tr>
<tr><td>7.1.4. Hemoglobin Abnormalities</td><td>The sentence is changed as follows:
• A decrease in hemoglobin to ~~≤~~ ≤80 g/L (~~≤~~ ≤4.9 mmol/L),
• A decrease in hemoglobin from baseline* of ~~≥~~ ≥50 g/L,</td><td>For clarity and consistency</td></tr>
<tr><td>7.1.5. Start of a Strong CYP3A4 Inducer/Strong CYP3A4 Inhibitor</td><td>The section title is changed:
Start of a ~~Strong CYP3A4 Inducer/~~Strong CYP3A4 Inhibitor / Moderate Dual CYP3A4/CYP2C9 Inhibitors

Removed description of a strong CYP3A4 inducers and the sentence is changed as follows:
If any strong inhibitors of CYP3A4 are given, macitentan must be interrupted from first dose of strong CYP3A4 inhibitor and until 4 weeks after the last dose of strong CYP3A4 inhibitor.</td><td>To allow continued administration of macitentan in the presence of strong CYP3A4 inducers since low exposure to macitentan is better than no exposure.</td></tr>
<tr><td>8. STUDY ASSESSMENTS AND PROCEDURES
Table 2</td><td>The frequency and volume of blood are changed as follows:
<table>
<tr><th></th><th>No. of Samples per Participant</th><th>Approximate Total Volume of Blood (mL)</th></tr>
<tr><td>Hematology</td><td>13 (for ≥ 2 years)
12 (for < 2 years)</td><td>15.6
~~15.6~~ to 14.4</td></tr>
<tr><td>Serum Chemistry</td><td>13 (for ≥ 2 years)
16 (for < 2 years)</td><td>15.6
19.2</td></tr>
<tr><td>~~Serum β hCG pregnancy tests~~</td><td>~~1.8~~</td><td>~~1.8~~</td></tr>
<tr><td>Loss by use of indwelling intra venous cannula</td><td>~~20~~ to 19 (for < 2 years)
~~17~~ to 19 (for < 2 years)</td><td>~~20.0~~ to 19.0
~~17.0~~ to 19.0</td></tr>
</table>
Total blood volume is changed as follows:
~~63.6~~ to 60.8 (for participants aged ≥2 years)
~~59.1~~ to 61.7 (for participants aged <2 years)

10 µL sampler / ≥ 2 years: ~~53.76~~ to 50.96
10 µL sampler / < 2 years: ~~53.70~~ to 56.30
20 µL sampler / ≥ 2 years: ~~53.92~~ to 51.12
20 µL sampler / < 2 years: ~~53.80~~ to 56.40</td><td>To align with exclusion criteria
To align with JNJ requirements for liver safety assessment. (For children < 2 years, liver function tests will be performed monthly during the study.)</td></tr>
<tr><td>8. STUDY ASSESSMENTS AND PROCEDURES</td><td>The sentence is changed as follows:
Sample patient diary</td><td>For clarity and consistency</td></tr>
</table>

Section number and Name	Description of Change	Brief Rationale
Study-Specific Materials		
8.3.4. Clinical Safety Laboratory Assessments (1.3. Schedule of Activities (SoA) Clinical Laboratory Tests)	The following sentence is added: **In all patients, laboratory tests must be monitored monthly for the first 6 months of study period and at each scheduled visit (every 12 weeks) until EOS. In addition, for patients of < 2 years, liver tests must be monitored monthly until EOS.**	To align with JNJ requirements for liver safety assessment.

Amendment 2 (25 November 2021)

Overall Rationale for the Amendment: The main reason for this protocol amendment is to modify the amount of blood collected and to add time points for blood collection in pediatric patients < 2 years. Minor corrections and editorial revisions are also being implemented.

The updates are indicated in bold for new text and strike-through for deleted text in the following table.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis PHARMACOKINETIC EVALUATIONS SAFETY EVALUATIONS	The following sentence is added: **The timepoints of blood collection will be determined by the age at the start of administration.** PK sampling time points for trough concentrations are changed as follows: For participants <2 years old, the blood samples will be drawn at the following timepoints: 2, 5, and 24 hours (before macitentan intake the next day) postdose on Day 1. A trough sample will be drawn at steady state (Visit ~~3~~**4 and Visit 5**). The sentence is changed as follows: Serum chemistry, including sodium, potassium, ~~chloride,~~ glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), total and direct bilirubin, alkaline phosphatase (AP), creatinine, and calcium	For clarity and consistency To assess the intra-subject variability of trough concentrations for participants <2 years old. For clarity and consistency
1.3. Schedule of Activities	PK sampling time points for trough concentrations are changed as follows: j. At Day 1, the blood samples for the PK profiling must be drawn at the following timepoints: 2 h, 5 h, and 24 h (before macitentan intake the next day) postdose. A trough sample (ie, predose) will be drawn on Visit ~~3~~**4 and Visit 5**. Samples for PK assessment should be collected within 20% deviation from the nominal sampling time. The following abbreviations is deleted: ~~DNA=deoxyribose nucleic acid;~~	To assess the intra variability of trough concentrations for participants <2 years old. For clarity and consistency
4.2.1. Study-Specific Ethical Design Considerations	The sentence is changed as follows: The total blood volume (approximately ~~45~~ **65** mL per participant will be collected through Week 52) to be collected. ~~is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the blood donation rule by the Japanese Red Cross Society.~~	To align with revises the amount of blood volume For clarity and consistency
6.1. Study Intervention	The following sentence is added to footnote:	Minor updates to

Section number and Name	Description of Change	Brief Rationale
Administered	**CSF (clinical service form) may be used depending on the results of the FMI stability study**	incorporate latest information
8 STUDY ASSESSMENTS AND PROCEDURES Overview Sample Collection and Handling	The sentence is changed as follows: • For each participant, the maximum amount of blood drawn from each participant in this study will not exceed ~~133~~ **65** mL. • After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, ~~United States Pharmacopeia (USP)~~ or sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock.	To align with revises the amount of blood volume For clarity and consistency
Table 2	The sentence is changed as follows: • Pharmacokinetic samples (if ~~an indwelling intravenous cannula~~ **the regular venous blood sampling is used**) The following No. of Samples per Participant are changed • PK samples (<2 years); 4 to **5** • Loss by use of indwelling intravenous cannula; ~~1~~ to **20 (≥2 years)**, ~~1~~ to **17 (<2 years)** Total blood volume is changed as follows: ~~44.6~~ to **63.6** (for participants aged ≥2 years) ~~42.6~~ to **59.1** (for participants aged <2 years) 10 µL sampler / ≥ 2 years: ~~40.76~~ to **53.76** 10 µL sampler / < 2 years: ~~40.68~~ to **53.70** 20 µL sampler / ≥ 2 years: ~~40.92~~ to **53.92** 20 µL sampler / < 2 years: ~~40.76~~ to **53.80**	For clarity and consistency Blood sampling time points were added to confirm intra-subject variability. Since an indwelling intravenous cannula is used for laboratory tests, the amount of blood lost was added.
8.3.2. Vital signs	Blood pressure and heart rate measurements will be assessed in supine, **sitting** or standing positions with a completely automated device. Manual techniques will be used only if an automated device is not available. In addition, throughout the study BP is tried to be measured on the same arm and in the same position (**supine, sitting or standing** ~~sitting or supine~~), using the same device by the same operator throughout the study for an individual participant.	For clarity and consistency
8.5. Quality of Life Assessments	The following word is added: The QoL will be assessed for participants of ≥2 years of age **at Day 1 (Visit 2)**.	For clarity and consistency
8.6.1. Evaluations	The following sentence is deleted: If CCI microsampling device CCI is used, peripheral blood samples of approximately 0.02 mL or 0.04 mL is needed for blood concentrations of macitentan and aprocitentan. ~~Peripheral blood samples will be collected via patients' finger.~~ The total of volume of blood samples are changed as follows: The total of volume of blood samples drawn for PK assessments would be 0.16 mL to 4.0 mL for participants aged ≥2 years and ~~0.08~~**0.10** mL to ~~2.0~~**2.5** mL for participants aged <2 years (Refer to Section 8). The following sentence is added:	To allow blood collection from other site than fingers To align the total blood volume with the PK sampling point change For clarity and

Section number and Name	Description of Change	Brief Rationale
	The timepoints of blood collection will be determined by the age at the start of administration. PK sampling time points for trough concentrations are changed as follows: For participants <2 years old, the blood samples will be drawn at the following timepoints: 2, 5, and 24 hours (before macitentan intake the next day) postdose on Day 1. A trough sample will be drawn at steady state (Visit ~~3~~**4 and Visit 5**).	consistency To assess the intra-subject variability of trough concentrations for participants <2 years old.
8.6.2. Analytical Procedures Pharmacokinetics	The sentence is changed as follows: If ~~an indwelling intravenous cannula~~ **the regular venous blood sampling method** is used, plasma samples will be analyzed.	For clarity and consistency
8.6.3. Pharmacokinetic Parameters and Evaluations	PK sampling time points for trough concentrations are changed as follows: Subjects <2 years of age: • ~~Steady State~~**At Week 4 and Week 8** (steady state): Predose Macitentan and Aprocitentan concentrations	To assess the intra-subject variability of trough concentrations for participants <2 years old.
9.4.5. Safety Analyses Vital Signs	The sentence is changed as follows: Vital signs including ~~temperature,~~ pulse/heart rate, ~~respiratory rate,~~ and blood pressure (systolic and diastolic) (supine, **sitting** ~~and~~ **or** standing) will be summarized over time, using descriptive statistics and/or graphically.	For clarity and consistency
10.12. Appendix 12: Study Conduct During a Natural Disaster STUDY VISITS	The sentence is changed as follows: • Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible by remote/virtually~~/flying nurse service~~/home visits.	Home nurse is not allowed at this study

Amendment 1 (2 November 2021)

Overall Rationale for the Amendment: The reason for this protocol amendment is to clarify that the treatment of PAH worsening is not limited to a specific drug, but within the scope of routine clinical practice.

The updates are indicated in bold for new text and strike-through for deleted text in the following table.

Section number and Name	Description of Change	Brief Rationale
6.8.1. Rescue Medication	Following text was modified: 'In the presence of PAH-worsening, any PAH specific treatment can be initiated per investigator's judgment. **If a participant initiates treatment with ERAs, study intervention (macitentan) must be discontinued (refer to Section 7.1)**.' ~~'In the presence of PAH-worsening, any PAH specific treatment (PDE5 inhibitor, riociguat, prostanoid) can be initiated per investigator's judgment.'~~	The specific drug name was deleted to clarify that it is within the scope of usual care.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	07-Aug-2023 03:42:44 (GMT)	Document Approval