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

# Macitentan / ACT-064992 / JNJ-67896062

# Pediatric PAH

# Protocol AC-055-312

## TOMORROW: pediaTric use Of Macitentan tO delay disease pRogRessiOn in PAH Worldwide

A multicenter, open-label, randomized study with single-arm extension period to assess the pharmacokinetics, safety and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension

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| EDMS no & version: | EDMS-RIM-264221, 4.0 |

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## SPONSOR CONTACT DETAILS

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|---|---|
| **SPONSOR** | Actelion Pharmaceuticals Ltd*<br>Gewerbestrasse 16<br>CH-4123 Allschwil<br>Switzerland<br>+41 61 565 65 65 |
| Clinical Trial Physician | Contact details of the Clinical Trial Physician can be found in the Investigator Site File |
| Medical Emergency Hotline<br><br>Toll phone number: [number] | Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File |

* Actelion Pharmaceuticals Ltd. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the Sponsor of the study

## CONTRIBUTORS TO THE PROTOCOL

| | |
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## CONTRACT RESEARCH ORGANIZATIONS INFORMATION

| | |
|---|---|
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| **COORDINATION OF BASELINE CHARACTERISTICS ADJUDICATION COMMITTEE** | Refer to the Investigator Site File. |
| **LAB SAMPLE COLLECTION AT SUBJECT'S HOME** | Refer to the Investigator Site File. |

A list of site-specific contact details for Contract Research Organizations (CROs) can be found in the Investigator Site File.

# INVESTIGATOR SIGNATURE PAGE

## Treatment name / number

Macitentan / ACT-064992 / JNJ-67896062

## Indication

Pediatric pulmonary arterial hypertension

## Protocol number, study acronym, study title

AC-055-312, TOMORROW; A multicenter, open-label, randomized, study with single-arm extension period to assess the pharmacokinetics, safety and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (eCRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the Sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Independent Ethics Committee or institutional review board (IEC/IRB) prior to study start and signed informed consent from parent(s) / legally designated representative of all subjects included in this study. Furthermore, I will obtain assent from developmentally capable children before entering them into this study. For subjects who come of age during their participation in this study I will obtain a separate consent. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment. If a protocol amendment leads to a change to the ICF I will re-consent the parent(s) / legally designated representative. I will allow direct access to source documents and study facilities to Sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment supplied by the Sponsor is being used only as described in this protocol. I will ensure that all parents or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual subject. I confirm herewith that the Sponsor is

allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

I participate in the Pharmacokinetics (PK) substudy: ☐

☐ I do not participate in the PK substudy:

*Initial the option that applies.*

| | **Country** | **Site number** | **Town** | **Date** | **Signature** |
|---|---|---|---|---|---|
| **Principal Investigator** | | | | | |

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| **DOCUMENT HISTORY** | |
|---|---|
| **Document** | **Date** |
| Amendment 8, Version 9 | 23-Nov-2021 |
| COVID-19 Appendix (EDMS-RIM-265698, 5.0) | 16-Nov-2021 |
| Amendment 7, Version 8 | 25-Jan-2021 |
| Amendment 6, Version 7** | 16-Sep-2020 |
| COVID-19 Appendix (EDMS-RIM-265698, 4.0) | 17-Jun-2020 |
| Amendment 3.1, Version 4.1 | 17-Jul-2020 |
| Amendment 5, Version 6* | 10-Jun-2020 |
| Amendment 4, Version 5* | 20-Mar-2020 |
| Amendment 3, Version 4 | 13-Mar-2018 |
| Amendment 2, Version 3 | 25-Apr-2017 |
| Amendment 1, Version 2 | 13-Oct-2016 |
| Original Protocol, Version 1 | 01-Jul-2016 |

*Protocol Versions 5 and 6 were only submitted to US FDA as they were superseded by Version 4.1, which was an urgent safety measure.

**Protocol Amendment 6 Version 7 submission was halted after submission to Health Authorities in Austria, Canada, Portugal, and United States of America (USA), as it was superseded by Version 8.

## Amendment 8 Version 9 (23 November 2021)

### Overall Rationale for the Amendment:

The TOMORROW study was designed to enroll a sufficient number of children to observe at least 187 primary disease progression events. Given recruitment challenges and number of events observed, the study design has been amended from an event-driven study to a pharmacokinetics (PK), safety and efficacy study with a fixed study duration (calendar-driven analysis timepoints).

Furthermore, an open-label (OL) single-arm extension period (SAEP) which was planned as a separate study protocol has been integrated into the present study protocol to allow seamless transition of all subjects to macitentan treatment if this is considered in their best interest after the last efficacy analysis (in 2024).

For these reasons, the following elements of the study have been amended:

- The Core Period will continue until first quarter 2024 and study duration will therefore be up to 7 years (considering first subject randomized in November 2017 as study started). Based on current recruitment, it is anticipated to have approximately 200 subjects enrolled by that time.

- The single-arm extension period (SAEP) will start seamlessly after the Core Period.
- The primary objective of the TOMORROW study will be to describe PK of macitentan in pediatric patients with PAH.
- The secondary objectives of the TOMORROW study will be the evaluation of safety and efficacy of macitentan in pediatric pulmonary arterial hypertension (PAH) patients.
    - Consequently, previous primary endpoint has been changed to a secondary endpoint.
    - In addition, exploratory efficacy endpoints related to World Health Organization functional class (WHO FC), N-terminal-pro-brain natriuretic peptide (NT-proBNP), echocardiography and physical activity have been changed to secondary endpoints as described in the summary of changes table below.
    - The totality of the secondary endpoints will be used to evaluate the efficacy of macitentan in pediatric PAH.

In addition, the enrollment of the TOMORROW study has been extended to pediatric patients < 2 y.o. (i.e., age 1 month and older). The PK information collected in children ≥ 2 y.o. and adults enabled the dose selection for children < 2 y.o. Due to the rarity of this population, only few subjects < 2 y.o. are likely to be enrolled. Therefore, in order to assess macitentan in this population, they will be enrolled as a cohort in the macitentan arm without randomization. The endothelin receptor antagonist (ERA) cap and the exclusion criterion related to prior/concomitant use of macitentan at Visit 2 will not apply to them either.

The continuation of the TOMORROW study will allow the evaluation of safety and efficacy of macitentan in pediatric patients with PAH, and to characterize the pharmacokinetics of macitentan in the pediatric population.

In addition, to the clinical formulation of the study drug macitentan (0.5 mg, 2.5 mg and 5 mg dispersible tablets), the to-be-marketed image (1 mg and 2.5 mg dispersible tablets) has been introduced. This formulation (called ‘final market image’ or ‘FMI’) is also dispersible in water. A change in the tablet image is necessary for future commercial use to ensure that the different dose strengths of the pediatric dispersible formulation are easily distinguishable in order to minimize the risk for future dosing errors. The FMI will replace the clinical formulation once sufficient stability data is available and local approval, if applicable, has been obtained.

The summary of changes table for current amendment is provided below. The updates are indicated in bold and deletions in strikethrough, wherever possible.

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Title Page;<br>Investigator Signature Page;<br>Protocol Synopsis AC-055-312 (Design) | Study title was revised as:<br>'A multicenter, open-label, randomized, ~~event driven~~ study **with single-arm extension period** to assess ~~efficacy, safety and~~ **the** pharmacokinetics**, safety and efficacy** of macitentan versus standard of care in children with pulmonary arterial hypertension'. | To align with modified study design. |
| 1.3. Purpose and Rationale of the Study ;<br>3.2 Study Design Rationale | Study rationale was revised. | To align with modified study design. |
| Protocol Synopsis AC-055-312 (Objectives);<br>2.1 Primary Objective;<br>2.2 Secondary Objectives | Primary and secondary objectives were revised. | To align with modified study design. |
| Protocol Synopsis AC-055-312 (Design);<br>3.1 Study Design | • Text was added to indicate that the new cohort of children < 2 y.o. will be assigned to macitentan group without randomization.<br>• Information about two important milestones and 3 timepoints of study analysis which will be triggered by them was added.<br>• Text added to indicate that the Cohort of children < 2 y.o. may additionally be analyzed.<br>• Additional information about study duration, safety follow-up and probable continuation in open-label single-arm extension period (SAEP) for each participating subject was added.<br>• Text related to study conduct-related activities outsourced to Contract Research Organizations (CROs) was revised. | To assess macitentan in this rare population.<br><br>To comply with different requirements from Health Authorities.<br><br>To align with modified study design. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Protocol Synopsis AC-055-312 (Periods);<br>3.1. Study Design | • Text was added to indicate that for the cohort of children < 2 y.o., the screening period ends with confirmation of eligibility (i.e., age at Visit 2 is less than 2 years) and assignment of macitentan kit at Visit 2, or with screening failure.<br>• Content related to study period was revised as 'Core Period' which commences with Visit 2 and continues until the end of Core Period (EOCP) visit.<br>• Information about 'Survival Follow-up' was revised.<br>• Definition of EOCP visit was added.<br>• Definition of 'Survival Follow-up' was revised.<br>• Details for additional ' Single-arm Extension Period (SAEP)' were added.<br>• Text corresponding to 'Study closure announcement' was deleted, wherever applicable.<br>• End of study (EOS) was redefined to indicate that EOS will happen at the end of SAEP.<br>• Also, information was updated to include the eligibility of a subject to participate in a post-trial access (PTA) or long-term extension (LTE) study and to clarify that subjects entering PTA or LTE study will not have a safety follow-up call in TOMORROW since their safety follow-up continues in the respective PTA or LTE study. | As the subjects < 2 y.o will not be randomized and will be assigned to macitentan arm to assess macitentan in this rare population.<br><br>To align with modified study design.<br><br>To clarify the post-trial access of macitentan and to clarify the reporting of AEs/SAEs after transitioning to post-trial access program. |
| Protocol Synopsis AC-055-312 (Planned Duration);<br>3.1. Study Design | • Text was updated to indicate that the current study is a calendar-driven study and study duration depends on dates to meet | To indicate change in study duration per modified study design. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | regulatory commitment and individual study duration will be based on the time of enrollment.<br>• Also, it was clarified that the overall study duration (including the Core Period and extension period) will be a minimum of 7 years (from first subject screened until last subject last EOS visit). | |
| Protocol Synopsis AC-055-312 (Subjects/Groups);<br>3.1. Study Design | • Previous information related to study sample size in terms of number of subjects to observe 187 primary endpoint events (i.e., 300 subjects) was deleted and updated with **'Approximately 200 subjects and no more than 300 subjects will be enrolled in this study based on feasibility.'**<br>• Cohort of children < 2 y.o. will not be randomized but will directly enter into the macitentan arm and ERA cap does not apply to this cohort. | To adjust as per new study design.<br><br>To ensure that the data on macitentan (and not on standard of care [SOC]) is generated in this rare subpopulation. |
| Protocol Synopsis AC-055-312 (Inclusion Criteria);<br>4.3. Inclusion Criteria | • Inclusion criterion # 2 was updated to include lower age limit as **≥1 month** (instead of ≥ 2 years).<br>• Inclusion criterion # 3 was updated to include lower weight limit as **≥ 3.5 kg** (instead of ≥ 10 kg). | To enroll children < 2 y.o. for whom the daily macitentan dose has been determined. |
| Protocol Synopsis AC-055-312 (Exclusion Criteria);<br>4.4. Exclusion Criteria | • New exclusion criterion # 5 was added to indicate that subjects with known diagnosis of bronchopulmonary dysplasia will be excluded.<br>• Following criteria were renumbered.<br>• Exclusion criterion # 8 is applicable to only children with ≥ 2 y.o. | To ensure that the infants entering in current study are not premature.<br><br>To clarify that children < 2 y.o. are allowed to enter on macitentan. |
| Protocol Synopsis AC-055-312 (Study Treatments); | • Text was updated to introduce the FMI and clarify how it will replace the clinical formulation. | To account for the new tablet image and dose strengths introduced. As the current |

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 5.1.1. Investigational treatment: Macitentan-description and rationale;<br>5.1.5. Macitentan administration | • A new table of number of tablets to be dispersed to attain a daily dose for the cohort of children < 2 y.o. was added.<br>• In addition to body weight, **age** of the subject will be verified every 12 weeks and this information will also be used for potential dose adjustment.<br>• Following statement was added: '**In subjects < 2 years of age, oral/ inhaled prostanoid treatment are also allowed as PAH-specific background therapy in all study periods.**' | clinical formulation does not provide differentiation across dose strengths a "to be marketed image" (different size, shape and deboss across dose strengths) has been introduced.<br><br>To account for the dosing regimen in children < 2 y.o. |
| Protocol Synopsis AC-055-312 (Concomitant Therapy);<br>5.2.4. Allowed concomitant therapy;<br>5.2.5. Forbidden concomitant therapy;<br>5.2.6. PAH treatment escalation | • Information about permitted concomitant medications during SAEP was added.<br>• Following statement was added: '**Concomitant use of an ERA (e.g., bosentan, ambrisentan) with macitentan is forbidden during entire study duration.**'<br>• Text added to indicate that that the use of macitentan is allowed only for participant of < 2 y.o. during Screening and before study entry.<br>• Forbidden concomitant medications to be prohibited to avoid drug-drug interactions (DDI) '**in the SAEP until EOS**.' This update was made, wherever applicable.<br>• Systemic administration of moderate dual CYP3A4/CYP2C9 inhibitors alone or in combination is additionally forbidden **in the SoC arm from 4 weeks before crossing over to macitentan and until EOM and in the SAEP until EOS**.<br>• PAH treatment escalation to be employed only **in the presence of** | To update information and new rules applicable to SAEP per modified study design.<br>To clarify that concomitant administration of 2 ERA treatments is forbidden.<br><br>To clarify which medications are allowed in the cohort < 2 y.o.<br><br>To allow continued administration of macitentan in the presence of strong CYP3A4 inducers since low exposure to macitentan is better than no exposure. |

| Section Number and Name | Description of Change | Brief Rationale |
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| | **disease progression defined per protocol** as per judgment of the investigator.<br>• Also, it is specified that '**During the SAEP, PAH treatment can be escalated as per local practice**.' | |
| Protocol Synopsis AC-055-312 (Endpoints);<br>6.1. Efficacy endpoints;<br>6.2. Safety endpoints | Primary, secondary and exploratory efficacy endpoints were revised as follows:<br>• The pharmacokinetic (PK) endpoints (same definition of PK endpoints defined since Protocol V1) have been updated as the primary endpoints.<br>• In addition to other secondary endpoints, previous primary endpoint (i.e., the time to Clinical Event Committee [CEC]-confirmed disease progression events) has become a secondary efficacy endpoint and retains the same definition since Protocol V1.<br>• The previous exploratory efficacy endpoints N-terminal pro-brain natriuretic peptide (NT-proBNP), WHO FC, echocardiography, accelerometry as well as the quality of life (QoL) endpoint related to Short Form (SF)-15 have become secondary efficacy endpoints.<br>• Exploratory efficacy endpoints were revised.<br>• Additional safety endpoint of 'AEs of special interest' was added in the existing list of the safety endpoints. Also, it was stated that '**These endpoints are assessed up to EOS.'**(previously mentioned as 'up to randomized macitentan or SOC + 30 days). | To align with modified study design. |

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Protocol Synopsis AC-055-312 (Assessments) | A reference to new tables (Table 2 and 3 corresponding to 'Visit and assessment schedule during Core Period for cohort of children < 2 y.o.' and 'Visit and assessment schedule during single-arm extension period', respectively) was added. | To align with modified study design.(cohort of children < 2 y.o. and SAEP). |
| Protocol Synopsis AC-055-312 (Statistical Methodology) | • Analysis sets and statistical analyses for primary and secondary efficacy endpoints as well as exploratory and pharmacokinetic endpoints were revised.<br>• New information about additional PK sets was included.<br>• Text was added to indicate that the safety endpoints for the cohort of children < 2 y.o. will be summarized separately. | To align with modified study design. |
| Protocol Synopsis AC-055-312 (Study Committee);<br>3.4. Study committees | • Content corresponding to Independent Statistical Analysis Center (ISAC) was revised to indicate that ISAC will no more perform the formal analysis for early efficacy or futility.<br>• Also, other statements were updated as follows:<br>o ISAC will monitor, in collaboration with the IDMC, the number of ~~primary efficacy endpoint~~ **disease progression** events occurring over time~~, in order to make appropriate predictions for Study Closure announcement date~~.<br>o A Clinical Event Committee (CEC), an independent committee of PAH experts (including pediatricians), will review and adjudicate in a blinded fashion the ~~primary~~ secondary endpoint**s related** | To align with modified study design. |

| Section Number and Name | Description of Change | Brief Rationale |
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| | **to disease progression** ~~of the study~~ according to the CEC Charter.<br>o An independent BCAC will centrally review and confirm eligibility of subjects with co-incidental congenital heart disease before their randomization **(before macitentan start for children < 2 y.o.)** as described in the BCAC Charter. | |
| Protocol Synopsis AC-055-312 (PK Substudy) | It was clarified that the modeling and simulation were performed based on the PK data **from pediatric subjects older than 2 years and adults** to select the appropriate daily dose in subjects below 2 years of age. | To provide background information used for selection of appropriate daily dose for subjects < 2 y.o. |
| Protocol Synopsis AC-055-312 (Study Extension);<br>3.1. Study Design | Study extension-related content was deleted. | As the study design has been revised to include SAEP, this content is not applicable anymore. |
| Protocol Synopsis AC-055-312 (Table 1) | • Table 1's heading was revised as: 'Visit and assessment schedule **during Core Period for subjects ≥ 2 years of age'**.<br>• Content of the table was revised to include new details of **EOCP** and **analysis 1 and 2 cut-off dates**. | To align with modified study design. |
| Protocol Synopsis AC-055-312 (Table 2 and 3) | New tables (Table 2 and 3) corresponding to visit and assessment schedule for cohort of children < 2 y.o. during Core Period and SAEP were added. Also, accordingly subsequent table numbers were updated. | To include information about visit and assessment schedule per modified study design. |
| 1.2.2. Benefit-risk Assessment for Participation in This Clinical Trial | • Following statement was deleted: ' ~~Children of at least 2 years of age and adolescents are at a more advanced developmental stage compared to suckling juvenile rats.~~' | Since study has been amended to allow enrollment of children < 2 y.o. |

| Section Number and Name | Description of Change | Brief Rationale |
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| | • Section was updated with information corresponding to background and rationale for including pediatric population < 2 years of age and proposed macitentan dosing regimen to be used in these pediatric subjects. | |
| 3.1. Study Design (PK assessment for Subjects < 2 y.o.) | New content was added to indicate that all subjects < 2 y.o. receiving macitentan will have PK assessments and this subpopulation PK analysis will be reported separately. Additional information about sampling and data analysis is also included. | To allow adequate characterization of macitentan PK and dose regimen in this age cohort. |
| 3.1. Study Design (Figure 1) | Figure 1 and underlying abbreviations and footnotes were revised to implement information about Core Period, EOCP, SAEP and EOS-related updates. | To align with modified study design. |
| 3.2. Study Design Rationale | Added information about rationales for revisions made to previous study design. | To provide appropriate justifications for implemented revisions. |
| | Added information about Sponsor representatives who are completely or partially blinded to study results. | To provide brief details about the content of Firewall Charter. |
| 4.1. Subject Population Description; | • Study population age range was revised as **≥ 1 month to < 18** years (from previous range of ≥ 2 years to <18 years).<br>• Following statement was added: '**Cohort < 2 y.o. is allowed to enter on macitentan**.' | To allow enrollment of children < 2 y.o. |
| 4.5.2. Acceptable Methods of Contraception | Following statement was added: '**Subjects in the SoC group who initiate macitentan study treatment (i.e., at Cross-over or at EOCP) must use either Option 1, 2 or 3.**' | To clarify methods of contraceptions, the female subjects from SoC group must opt for after cross-over/EOCP. |
| 5.1.1. Investigational Treatment: Macitentan - Description and Rationale | • Added information about PK profile assessment in the cohort of children < 2 y.o.<br>• Added following statement: | To provide instructions for the new cohort of children < 2 y.o. |

| Section Number and Name | Description of Change | Brief Rationale |
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| | '**After EOCP (i.e., during SAEP) those medications can be initiated at any time.**' | To indicate that the forbidden PAH medications (PDE5i, ERA, prostanoid) can be initiated during SAEP for the new cohort of children < 2 y.o. |
| 5.1.3.Treatment Assignment | Added information about treatment assignment for the cohort of children < 2 y.o. | To provide instructions for the new cohort of children < 2 y.o. |
| 5.1.5. Macitentan Administration | It was clarified that the macitentan will be administered after dispersion of tablets in water for all subjects. | To update information based on new dispersible tablet formulation. |
| | Following text was added: '**For cohort of children < 2 y.o., the parent(s) / legally designated representative is instructed not to administer macitentan at Week 4 and Week 8 visits until the pre-dose PK sample has been collected.**' | For appropriate collection of pre-dose PK sample in this study population. |
| 5.1.6.3. Macitentan Dispensing | Statement was revised as follows: 'The subjects will receive enough macitentan to cover the period up to the next scheduled 12-weekly visit (i.e., excluding Visit 3 for PK) **during Core Period, or 24-weekly visit during SAEP, respectively**.' | To ensure that subject receives enough macitentan till EOT. |
| 5.1.8. Macitentan dose adjustments and interruptions | Statement was revised as follows: 'Macitentan dose adjustments other than for change in **age category for subjects of < 2 y.o. and for** weight category **for subjects at least 2 y.o.** are not permitted.' | To provide instructions for the new cohort of children < 2 y.o. |
| 5.1.9. Macitentan: Premature Discontinuation of Study Treatment | Section was updated to include information about 'premature discontinuation during Core Period' and to indicate that the vital status will be collected at least yearly (i.e., survival FU) until the cutoff date for Analysis 2. | To align with modified study design. |
| 6.3. Quality of Life endpoints | • Quality of life endpoints will be assessed **only** in English-speaking | To align with modified study design. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | subjects in the USA, **up to end of randomized macitentan or SoC+ 7 days.**<br>• Assessment using PedsQL™4.0 Generic Core Scale Short Form (SF15), was deleted from this section.<br>• Following text was added: '**For the cohort of children < 2 y.o., this questionnaire is not available.**' | Per revised study design, this endpoint is considered as a secondary endpoint and included in respective section.<br><br>Not applicable to this specific study population. |
| 6.4. Other Pharmacokinetic Endpoints | Content of the section was updated. | To align with modified study design. Trough PK has become primary endpoint. |
| 7.3. Efficacy Assessments | Statement referring to Sections 6.1.1 and 6.1.2 was deleted. | No longer applicable due to revision of primary and secondary endpoints. |
| 7.3.5. 6-minute Walk Test | Following statement was revised as: 'The 6-minute walk distance (6MWD) will be assessed in subjects ≥6 years of age who understand and are able to perform the test correctly [Douwes 2015, Takatsuki 2013b] **and who can perform the test per protocol at randomization**.' | To clarify that this test will only be done if baseline (Randomization/ Visit 2) 6MWD can be done. |
| 7.4.3. Physical Examination | Following statement was added to existing text: '**During SAEP, the physical examination will only be documented in the subject's medical chart and not in the eCRF. Abnormal observations must be reported in the AE pages of the eCRF.**' | To provide appropriate guidance for documentation of information related to physical examination during SAEP. |
| 7.4.5.1. Type of Laboratory | Following statement was added to existing text: '**For monthly liver and hemoglobin/hematocrit tests, a local laboratory may be used if normal ranges are available for the given age group of the subject. Respective local laboratory results, will be entered into the eCRF together with the respective normal ranges.**' | To allow for use of local laboratory for monthly liver and hemoglobin/hematocrit tests under specific circumstances. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.4.5.2. Laboratory Tests | • Following statement was added to existing text: '**In subjects < 2 y.o., liver tests must be monitored monthly for the first 12 months of study period and at each scheduled visit (every 12 weeks) thereafter until EOS**.'<br>• Statement was revised to indicate that hemoglobin and hematocrit and liver aminotransferase s(AST/ALT) levels must be monitored monthly for the first 6 months of macitentan treatment and **every 12 weeks thereafter**. | To align with JNJ requirements for liver safety assessment.<br><br>To aid in deciding the interruption of macitentan study treatment. |
| 7.5. Palatability and Acceptability of Macitentan Drug Formulation | Following statement was revised as: 'The site study personnel will record the score **and the method of administration (e.g., spoon)** in the eCRF.' | To capture additional data about method of study intervention administration. |
| 7.6. Quality of Life Assessments | Following statement was added to existing text: '**Below that age the selected questionnaires are developmentally not appropriate and are thus not collected.**' | To indicate why QoL questionnaires are not collected for subjects < 2 years of age. |
| 7.7.1. Timing for PK Sampling | Text was updated as follows:<br>'In all subjects **who are 2 y.o. and older** randomized to macitentan and receiving macitentan, a trough sample (i.e., pre-dose) will be drawn on Visit 4 (Week 12) for PK assessments.'<br><br>**'In subjects younger than 2 y.o., samples will be drawn at 2h, 5h, and 24h after the first macitentan dose at Visit 2. Trough samples (i.e., pre-dose) will be drawn on Week 4 and 8 (refer to 7.7.2 Procedures for sampling for details).'** | To specify that the substudy only applies to subjects at least 2 years-old.<br><br>To introduce age-appropriate PK sampling for children < 2 y.o. |

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 7.7.2. Procedures for Sampling | New instructions for PK sampling in age cohort < 2 years of age were introduced.<br><br>Detailed instructions on sample manipulation were deleted. | To introduce age-appropriate PK sampling for children < 2 y.o.<br><br>To avoid duplicating instructions available in the laboratory manual. |
| 7.7.3. Labeling;<br>7.7.5. Shipping procedures (previous sections) | These subsections were deleted and other subsections were renumbered accordingly. | As the information will be updated in central lab document and not in the protocol, to allow more flexible information recording. |
| 7.7.3. Bioanalysis | Section was revised. | To update information. |
| 7.7.4. Total blood volume | Section was revised. | To update information. |
| 8. Schedule of Visits | Following text was added: '**During the SAEP unscheduled visits are not recorded in the eCRF but (S)AE are reported, if applicable.**' | To indicate that SAEs must be reported in SAEP. |
| 8.1. Screening / Visit 1 | Following text was added: ' **For the cohort of children < 2 y.o. screening ends with confirmation of eligibility and assignment of macitentan kit at Visit 2, or with screening failure.**' | To provide information about screening completion for the cohort of children < 2 y.o. |
| 8.2. Randomization / Visit 2 (Day 1) | A new assessment was added: ' **for children < 2 y.o.: PK samples at 2h, 5h, and 24h after the first macitentan dose'**. | To provide information about the cohort of children < 2 y.o. |
| | Following text was added: '**For subjects < 2 y.o. age will be used by IRT system to calculate the daily dose of macitentan.**' | |
| | Following text was added:<br>'**For subjects < 2 years of age at Visit 2:**<br>**For PK assessment, approximately 1.7 mL of blood (including dried blood samples via Neoteryx Mitra™ device where the use of this sampler is allowed per local requirements) are collected at 3 timepoints after** | |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | **the first dose of macitentan as described in Section 7.7.1.**' | |
| 8.3. PK Visits at Week 4 and Week 8 for Subjects < 2 Years of Age | New section added. Following subsections were renumbered | To account for the extra visits in children < 2 y.o. for PK sample collection. |
| 8.10. Cross-over Visit | A new eligibility criteria for severe liver injury and severe renal impairment was added to determine eligibility of a subject to cross-over to macitentan treatment. | To account for all safety eligibility criteria relevant for macitentan treatment. |
| 8.11. Unscheduled Visits | Following text was added: '**During SAEP, the only data collected and reported as part of an unscheduled visit are (S)AEs and if applicable laboratory re-tests as requested in Section 5.1.10.**' | To indicate that only AE-SAE-related safety data will be collected on unscheduled visit in SAEP. |
| 8.13. End of Core Period (EOCP);<br>8.14. Single-arm Extension Period (SAEP) | New sections were added to include relevant information about corresponding study visits. Following subsections were renumbered. | To align with modified study design. |
| 8.15. End of Study | Section was revised. | To align with modified study design. |
| 8.16. Safety Follow-up;<br>9.4. Medical Care of Subjects After Study Completion/Withdrawal from Study | Section was revised to clarify about safety follow-up procedure in case of subjects who will be transitioned to PTA or LTE study by Janssen. | For clarification. |
| 8.17. Survival Follow-up | Timepoints for collection of survival follow-up data before Analysis 1 and 2 was clarified. | To account for modified study design. |
| 9.1. Study Completion | Content was revised as follows:<br>'The clinical database~~, the CEC database, and the central laboratory databases are~~ **is** locked after all data collected up to last subject last visit/contact have been collected and are considered accurate.<br>~~Subjects who are already in screening at announcement of Study Closure will be handled as screening failure.~~' | To align with modified study design. |

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 9.2. Premature withdrawal from study, premature study visit discontinuation | The term 'study closure' was replaced with 'EOCP', wherever applicable.<br><br>New content about ' Premature study discontinuation during Single-Arm Extension Period' was added. | To align with modified study design.<br><br>To give instructions for the new study period. |
| 10.1.4. Reporting of Adverse Events;<br>10.2.2. Reporting of Serious Adverse Events;<br>10.3.1. Reporting of Pregnancy | Following statement was added:<br>'**Subjects who enter a PTA or LTE study at EOS will be waived from the safety follow-up call since they will be monitored in the respective PTA or LTE study.**' | To avoid double safety reporting for subjects who will be transitioned to continued access program. |
| 10.1.4. Reporting of Adverse Events | Following statement was added:<br>'**Single-Arm Extension Period: During SAEP all exacerbations of underlying disease will be reported on the AE form.**' | To give instructions for the new study period. |
| 10.2.2. Reporting of Serious Adverse Events | Following statement was added:<br>'**During the SAEP disease progression events will be reported in the AE section of the eCRF and, if classified as "serious," on an SAE form.**' | To give instructions for the new study period. |
| 10.2.3. Follow-up of Serious Adverse Events;<br>10.2.4. After the Study Period and Safety Follow-up Period;<br>10.2.5. Reporting Procedures | Content was added to indicate that **during SAEP the investigator will report all SAEs directly to the Sponsor within 24 hours of their knowledge.** | To give instructions for the new study period. |
| 10.2.5. Reporting Procedures | Content was amended as follows:<br>• 'The SAE forms must be sent to the CRO **during Core Period** (contact details are provided on the SAE form), **while they will be sent directly to the Sponsor during SAEP**.'<br>• 'The CRO personnel **(or Sponsor personnel during SAEP)** may contact the investigator to obtain further information as instructed by the Sponsor.' | To give instructions for the new study period. |

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 10.3.1. Reporting of Pregnancy;<br>10.3.2. Follow-up of Pregnancy | Content was updated with following details:<br>• 'Any pregnancy must be followed up to its conclusion and the outcome must be reported to the CRO on the **applicable pregnancy notification form.**<br>• **During SAEP the pregnancy is reported directly to the Sponsor**.' | To account for new pregnancy forms used by the Sponsor.<br><br>To give instructions for the new study period. |
| 11. Statistical Methods | Content was deleted from here and moved to Section 3.2:<br>'The Sponsor representatives preparing and reviewing the Statistical Analysis Plan (SAP) for the Randomized Period will remain blinded until the Analysis 1 results are available.' | To align with modified study design. |
| 11.1.2. Full Analysis Set | Information about FAS2 and FAS3 was included. | |
| 11.1.3. Per Protocol Set | Section was deleted and following sections were renumbered. | |
| 11.1.4. Pharmacokinetic Analysis Sets | New PK analysis sets were added. | To cover the age cohort of children < 2 y.o. |
| 11.1.5. Usage of the Analysis Sets | Use of analysis sets were further specified.<br><br>Statement related to per protocol set (PPS) was deleted. | To cover analysis of cohort of children < 2 y.o. and new study periods.<br><br>To align with modified study design. |
| 11.2.1. Primary Efficacy Variable | Section was renamed (previously 'Primary efficacy variable') and updated with relevant information about new primary variable. | To align with modified study design. |
| 11.2.2. Secondary Efficacy Variables | A new secondary efficacy variable 'Time to first CEC-confirmed disease progression' was added. Also, few exploratory variables which are now considered as secondary variables per modified study design, were moved in this section. | To align with modified study design. |

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 11.2.3. Exploratory Variables;<br>11.2.4. Safety Variables;<br>11.2.5. Quality of Life at Each Timepoint of Assessment;<br>11.2.6. Pharmacokinetic Variables | Sections were updated. | To align with modified study design. |
| 11.3. Description of Statistical Analyses | Subsection on overall testing strategy was deleted and next subsection was renumbered. | To align with modified study design. |
| 11.3.1. Analysis of the Primary Variable | Section was revised to include updates of new primary variable. | To align with modified study design. |
| 11.3.2. Analysis of the Time to Event Secondary Efficacy Variables | A new Section 11.3.2 was added to include information about main, supportive and subgroup analyses and handling of missing data for 'time to event secondary efficacy variables.' | |
| 11.3.3. Other Secondary Efficacy Variables | A new section was added to include additional revised secondary efficacy variables. | To align with modified study design. |
| 11.3.4. Analysis of the Exploratory Variables | Subsections 11.3.4.1 (WHO FC I or II), 11.3.4.2 (Percent of Baseline in plasma NT-proBNP), 11.3.4.4 (Physical activity) and 11.3.4.5 (Echocardiography variables) were moved to Section 11.3.3 (Other secondary efficacy variables) and remaining subsections were renumbered. | |
| 11.3.5.1. Adverse Events ;<br>11.3.5.2. Laboratory Variables | Updated information about analysis of safety variables for SAEP. | |
| 11.4. Interim Analysis | Section was revised to include new timepoints of study analysis and content related to 'group sequential design' and Table 5 was deleted. | |
| 11.5. Sample Size | All subsections (Section 11.5.1 to 11.5.5, including Tables 6 to 9) were deleted and following statement was added: | |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | '**The sample size of approximately 200 subjects and not more than 300 subjects is driven by feasibility and no formal sample size calculations are provided. The study recruitment will be closed by Q4 2023 to allow at least 12 weeks study follow-up for Analysis 2 in Q1 2024. Analysis 1 and 2 are driven by the regulatory timelines.**' | |
| 12.1. Data Collection | Content was updated to indicate that the third party (CRO) will carry out the data management and the Sponsor will work with the CRO following a detailed oversight plan to ensure that oversight of quality is maintained. | To avoid repetition in the protocol document. |
| 12.3. Database Management and Quality Control | Unnecessary information was deleted and the text was revised. | Since data hand over is governed by contractual agreement between Sponsor and CRO and not by the protocol; to improve the clarity. |
| 13.3. Informed Consent | Following statement was added: **'If the female partner of a male participant becomes pregnant, an informed consent will be obtained prior collecting the information on pregnancy. For pregnant partners who are not yet of legal age, the consent will be obtained from parent(s)/ legally designated representative and assent will be obtained from the partner.'** | To provide information about obtaining an informed consent/assent form in case of pregnancy. |
| 14. References | List of references was updated with 2 new references and corresponding references are cited in main protocol, wherever applicable. | To provide supporting information. |
| Throughout the protocol | • The term 'event-driven' was either deleted or replaced with 'calendar-driven,' wherever applicable.<br>• 'previous EOS was replaced with 'EOCP (last visit with efficacy assessment),' wherever applicable | For clarity and consistency; minor errors were noted. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | and new EOS was introduced (last visit of SAEP).<br>• 'Primary Endpoint Event' was replaced with 'per protocol disease progression'.<br>• Minor corrections and editorial revisions were made. | |

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# LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| 6MWD | 6-minute walk distance |
| 6MWT | 6-minute walk test |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{\tau}$ | Area under the plasma concentration-time curve during one dosing interval |
| BCAC | Baseline Characteristics Adjudication Committee |
| BP | Blood pressure |
| CEC | Clinical Event Committee |
| CFR | Code of Federal Regulations (US) |
| CHD | Congenital heart disease |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CL | Confidence limits |
| $C_{max}$ | Maximum plasma concentration |
| CRA | Clinical Research Associate |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CYP | Cytochrome P450 |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EEA | European economic area |
| EMA | European Medicines Agency |
| EOM | End of macitentan |
| EOCP | End of core period |

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|---|---|
| EOS | End of study |
| ERA | Endothelin receptor antagonist |
| ET | Endothelin |
| FAS | Full Analysis Set |
| FC | Functional class |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HIV | Human immunodeficiency virus |
| hPAH | Heritable pulmonary arterial hypertension |
| HR | Hazard ratio |
| IV | Intravenous |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| ILSDRB | Independent Liver Safety Data Review Board |
| IP receptor | Prostacyclin receptor |
| iPAH | Idiopathic pulmonary arterial hypertension |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ISAC | Independent Statistical Analysis Center |
| ISF | Investigator site file |
| LAP | Left atrium pressure |
| LLN | Lower limit of normal range |
| LOQ | Limit of quantification |
| LTE | Long-term extension |
| LVEDP | Left ventricular end diastolic pressure |

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|---|---|
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mPAP | Mean pulmonary artery pressure |
| MRI | Magnetic resonance imaging |
| MVPA | Moderate to vigorous physical activity |
| NT-proBNP | N-terminal pro-brain natriuretic peptide |
| o.d. | Once daily |
| p.p. | Post-partum |
| PAH | Pulmonary arterial hypertension |
| PAH-aCTD | PAH associated with connective tissue disease |
| PAWP | Pulmonary artery wedge pressure |
| PDE-5 | Phosphodiesterase Type 5 |
| PH | Pulmonary hypertension |
| PI | Principal investigator |
| PK | Pharmacokinetics |
| PTA | Post-trial Access |
| $PVO_2$ | Peak oxygen consumption |
| PVR | Pulmonary vascular resistance |
| PVRi | Pulmonary vascular resistance index |
| QoL | Quality of Life |
| REVEAL | Registry to Evaluate Early and Long-Term PAH Disease Management |
| RHC | Right heart catheterization |
| RSI | Reference safety information |
| SC | Subcutaneous |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SAEP | Single-arm extension period |
| SE | Standard error |

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|---|---|
| SIV | Site initiation visit |
| SoC | Standard of Care |
| SOCBP | Subject of childbearing potential |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| SP | Study phase |
| $t_{½}$ | Terminal half-life |
| TAPSE | Tricuspid annular plane systolic excursion |
| TBIL | Total bilirubin |
| $t_{max}$ | Time to reach maximum plasma concentration |
| TOPP | Tracking Outcomes in Pediatric Pulmonary Hypertension Registry |
| ULN | Upper limit of the normal range |
| WHO | World Health Organization |

# PROTOCOL SYNOPSIS AC-055-312

| | |
|---|---|
| TITLE | A multicenter, open-label, randomized study with single-arm extension period to assess the pharmacokinetics, safety and efficacy of macitentan versus standard of care in children with pulmonary arterial hypertension. |
| ACRONYM | TOMORROW: pedia**T**ric use **O**f **M**acitentan t**O** delay disease p**R**og**R**essi**O**n in PAH **W**orldwide |
| OBJECTIVES | **Primary objective**<br>To evaluate the pharmacokinetics (PK) of macitentan in children with pulmonary arterial hypertension (PAH).<br>**Secondary objectives**<br>To assess safety and tolerability of macitentan in children with PAH.<br>To assess efficacy of macitentan in children with PAH. |
| DESIGN | This is a prospective, multicenter, open-label, randomized, controlled, parallel group, Phase 3 study with an open-label single-arm extension period to evaluate PK safety and efficacy of macitentan in children with PAH. Children < 2 years old (y.o.) will be assigned as a cohort to the macitentan group without randomization.<br>In consideration of the different requirements from Health Authorities, two important milestones (ie, fourth quarter of 2022 (Analysis 1), and first quarter of 2024 (Analysis 2), respectively) will trigger the analysis timepoints.<br>There will be three time points of study analysis:<br>• Analysis 1 of Core Period: with cutoff date in the fourth quarter of 2022.<br>• Analysis 2 of Core Period: with cutoff date in the first quarter of 2024.<br>• Analysis 3 final analyses including the core and the single-arm extension periods. |

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| | The sponsor will determine the cutoff date for the first two analyses three months prior to this date and will document the decision accordingly in the Trial Master File.<br><br>The cohort < 2 y.o. may be analyzed at additional timepoints in order to allow ongoing evaluation of benefit-risk in this vulnerable population.<br><br>Study duration for each individual subject will be based on their time of enrollment. All subjects are planned to remain in the study until the database lock in 2024 (Analysis 2). Thereafter, if it is considered in the best interest of the subject, continuation in the open-label single-arm extension period with macitentan will be offered.<br><br>In order to minimize potential bias related to the open-label design some aspects of the study conduct have been outsourced to Contract Research Organizations (CROs). The firewalls put in place between blinded and unblinded study team members are described in a dedicated Firewall Charter. |
| PERIODS | **Screening Period:** Starts from signed informed consent and ends with randomization or confirmation of screening failure (up to 6 weeks after signed informed consent).<br><br>Cohort of children < 2 y.o.: The Screening Period ends with confirmation of eligibility (i.e., age at Visit 2 is less than 2 years) and assignment of macitentan kit at Visit 2, or with screening failure.<br><br>**Core Period:** Commences with Visit 2 and continues until the End of Core Period (EOCP) visit.<br><br>Pre-Event Study Phase (Pre-Event SP): Starts from Visit 2 until disease progression event confirmed by the CEC or until EOCP visit, whichever comes first.<br><br>Post-Event Study Phase (Post-Event SP): Begins with CEC-confirmed event and continues until EOCP visit. During Post-Event SP PAH-specific background treatment may be escalated in both treatment arms as per local practice. Any additional treatment, including intravenous |

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| | (IV) or subcutaneous (SC) prostanoids may be used in both treatment arms. Subjects in the macitentan arm can continue receiving macitentan. Subjects in the SoC arm are offered to cross-over to macitentan treatment, if this is in their best interest per investigator judgment.<br><br>End of Macitentan (EOM)**:** All subjects treated with macitentan who prematurely discontinue macitentan will have an EOM visit within 1 week after the last dose of macitentan.<br><br>Survival Follow-up**:** Applies to subjects who prematurely discontinue regular study visits during Core Period. Survival data will be collected at least yearly after the last regular study visit and until EOCP for Analysis 2 . In these subjects the last survival follow-up contact constitutes their EOS.<br><br>End of Core Period (EOCP) Visit**:** This visit will occur in first quarter 2024 and before the cutoff date for Analysis 2 which will be announced by the sponsor. For subjects who don't enter the Single-Arm Extension Period (SAEP), the EOCP Visit constitutes their End-of-Study (EOS) Visit.<br><br>**Safety Follow-up Period:** Applies to subjects who prematurely discontinue macitentan or SoC treatment during Core Period or during the SAEP. In addition, it applies to subjects at EOS who do not enter the SAEP or who do not go into a post-trial access (PTA) or long-term extension (LTE) study. It begins immediately after premature end of treatment or after EOCP/EOS and ends at least 30 days later with a safety follow-up telephone call.<br><br>Subjects prematurely discontinuing treatment during Core Period are encouraged to continue participation in the study according to the regular study visit schedule or at least agree to Survival Follow-up until EOCP. Only for subjects whose parent(s) / legal representative withdraw consent to further study participation is the safety follow-up telephone call EOS.<br><br>**Single-arm Extension Period (SAEP):** This period starts at EOCP visit and ends at EOS visit. Subjects who are in the 12-weekly regular visits at EOCP visit, and for whom the |

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| | investigator judges that macitentan treatment could be beneficial and who fulfill the safety criteria to initiate or continue macitentan treatment are eligible to enter the open-label single-arm extension period.<br><br>End of Study (EOS) Visit**:** At the end of the SAEP each subject will come for an EOS visit within 12 weeks of the Sponsor announcing the end of the study. For subjects who discontinue the study prematurely the last visit or last survival FU contact constitutes their EOS visit.<br><br>For subjects who cannot access macitentan, a continued access program will be put in place (e.g., PTA, LTE study) to allow treatment continuation, if assessed beneficial by the investigator and within local regulations.<br><br>For subjects rolling over to a PTA or LTE study after the SAEP, the enrollment must occur on the day of the last visit of this study i.e., EOS visit, to avoid macitentan treatment interruption. These subjects will not have a safety follow-up call in TOMORROW since their safety follow-up continues in the respective PTA or LTE study.<br><br>The study is considered completed when the last subject completes the study (i.e., last EOS visit). |
| PLANNED DURATION | The study starts from first subject, first visit, defined as screening (i.e., ICF signed), and ends with last subject, last visit, defined as the last EOS visit.<br><br>This is a calendar-driven study and time points of analysis depend on dates to meet regulatory commitment.<br><br>Study duration for each individual subject will be based on their time of enrollment. All subjects are planned to remain in the study until the cutoff date for Analysis 2 in 2024. Thereafter, if it is considered in the best interest of the subject, continuation in the open-label single-arm extension period with macitentan will be offered. |

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| | Subject participation in the Core Period at timepoint of Analysis 2 will be up to 7 years. Participation in the SAEP will be at least 24 weeks.<br><br>Overall study duration (including Core Period and extension period) will be a minimum of 7 years (from first subject screened until last subject last EOS visit). |
| SITE(S) / COUNTRY(IES) | Approximately 90 sites in about 30 countries (planned). |
| SUBJECTS / GROUPS | Approximately 200 subjects and no more than 300 subjects will be enrolled in this study based on current feasibility.<br><br>Subjects ≥ 2 y.o. at Visit 2 will be randomized in a 1:1 ratio to either receive macitentan or continue SoC. Randomization is stratified by ongoing/planned endothelin receptor antagonist (ERA) treatment (yes vs no) and by WHO Functional Class (FC; FC I/II vs FC III) at randomization. In the central randomization system, the proportion of subjects with ERA treatment will be limited to a maximum of 40% of the overall number of randomized subjects.<br><br>Cohort of children < 2 y.o. will not be randomized but will enter directly into the macitentan arm. The ERA cap does not apply to this cohort. |
| INCLUSION CRITERIA | 1. Signed informed consent by the parent(s) or legally designated representative AND assent from developmentally capable children prior to initiation of any study-mandated procedure.<br>2. Criterion modified per Amendment 8 Version 9:<br>Males or females between ≥ 1 month and < 18 years of age.<br>3. Criterion modified per Amendment 8 Version 9:<br>Subjects with body weight ≥ 3.5 kg at randomization<br>4. Criterion modified per Amendment 6 Version 7: 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 |

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| | resistance index (PVRi) > 3 Wood Units x $m^2$), where in the absence of pulmonary vein obstruction and/or significant lung disease PAWP can be replaced by LAP or LVEDP (in absence of mitral stenosis) assessed by heart catheterization.<br>5. PAH belonging to the Nice 2013 Updated Classification Group 1 (including Down Syndrome) and of the following etiologies:<br>• Idiopathic PAH (iPAH)<br>• Heritable PAH (hPAH)<br>• PAH associated with congenital heart disease (CHD):<br>PAH with co-incidental CHD (confirmed by the Baseline Characteristics Adjudication Committee [BCAC])<br>Post-operative PAH (persisting/ recurring/ developing ≥ 6 months after repair of CHD)<br>• Drug or toxin-induced PAH<br>• PAH associated with HIV<br>• PAH associated with connective tissue disease (PAH-aCTD)<br>6. WHO FC I to III<br>7. PAH-specific treatment-naïve subjects or subjects on PAH-specific treatment (monotherapy or combination of two therapies)<br>8. Females of childbearing potential must have a negative pregnancy test at Screening and at Baseline, and must agree to undertake monthly pregnancy tests, and to use reliable method of contraception (if sexually active) up to EOS. |
| EXCLUSION CRITERIA | **Etiology**<br>1. Subjects with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn.<br>2. Subjects with PAH associated with open shunts, as specified below:<br>a. Eisenmenger syndrome |

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| | b. Moderate to large left-to-right shunts.<br>3. Subjects with the following congenital cardiac abnormalities:<br>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<br>b. Univentricular heart and/or subjects with Fontan-palliation.<br>4. Subjects with pulmonary hypertension due to lung disease (e.g., bronchopulmonary dysplasia).<br>5. Criterion added per Amendment 8 Version 9:<br>Subjects with known diagnosis of bronchopulmonary dysplasia.<br>**Treatment and intervention**<br>6. Subjects receiving a combination of > 2 PAH-specific treatments at randomization.<br>7. Treatment with IV or SC prostanoids within 4 weeks before randomization unless given for vasoreactivity testing.<br>8. Criterion modified per Amendment 8 Version 9: In children ≥ 2 y.o.: Previous treatment with macitentan at any time.<br>9. Treatment with another investigational drug within 4 weeks prior to randomization.<br>10. Any PAH-related surgical intervention planned, or subjects listed for organ transplantation related to PAH.<br>11. Treatment with strong inducers of cytochrome P450 3A (CYP3A4) such as rifabutin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort (hypericum perforatum), within 4 weeks prior to randomization.<br>12. Systemic treatment with strong inhibitors of CYP3A4 such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, |

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| | telithromycin, and voriconazole within 4 weeks prior to randomization.<br>13. Criterion modified per Amendment 3.1 Version 4.1: Systemic treatment with moderate dual CYP3A4/CYP2C9 inhibitor (e.g., fluconazole and amiodarone), or administration of a combination of a moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (e.g., miconazole, piperine) within 4 weeks prior to randomization.<br>**Baseline abnormalities**<br>14. Subjects with pulmonary vein stenosis.<br>15. Known concomitant life-threatening disease with a life expectancy < 12 months.<br>16. Hemoglobin or hematocrit < 75% of the lower limit of normal range.<br>17. Serum aspartate aminotransferase and/or alanine aminotransferase > 3 × upper limit of normal range.<br>18. Criterion modified per Amendment 6 Version 7: Severe hepatic impairment, e.g., Child-Pugh Class C.<br>19. Clinical signs of hypotension which in the investigator's judgment would preclude initiation of a PAH-specific therapy.<br>20. Criterion added per Amendment 6 Version 7: Severe renal insufficiency (estimated creatinine clearance < 30 mL/min or serum creatinine > 221 μmol/L).<br>**Pregnancy and breastfeeding**<br>21. Pregnancy (including family planning) or breastfeeding.<br>**Other categories**<br>22. Known hypersensitivity to ERAs, or any of the excipients.<br>Drug or substance abuse, or any condition that, in the opinion of the investigator, may prevent compliance with the protocol or adherence to study treatment. |
| STUDY TREATMENTS | **Macitentan arm**<br>Macitentan, open-label, is administered once daily via oral route in dispersed form. |

Clinical Formulation: Macitentan is provided as a dispersible tablet of following dosage strengths: 0.5 mg, 2.5 mg, and 5 mg. This formulation is only used in subjects of at least 6 months of age and will be controlled via IRT.

Clinical Formulation:

| Age [Months] | Body Weight [kg] | Daily dose | Number of tablets to be dispersed |
|---|---|---|---|
| ≥ 1 and < 6 | not applicable (NA) | NA | NA |
| ≥ 6 and < 24 | not applicable | 2.5 mg | 1×2.5 mg |
| ≥ 24 | ≥10 kg and < 15 kg | 3.5 mg | 2×0.5 mg & 1×2.5 mg |
| | ≥15 kg and < 25 kg | 5.0 mg | 1×5.0 mg |
| | ≥25 kg and < 50 kg | 7.5 mg | 1×2.5 mg & 1×5.0 mg |
| | ≥ 50 kg | 10.0 mg | 2×5.0 mg |

Final Market Image (FMI): Macitentan dispersible tablet will be available in new dose strengths of 1 mg and 2.5 mg with different shape and debossing. The FMI will replace the Clinical Formulation once sufficient stability data is available and local approval, if applicable, has been obtained. This formulation will be used in all subjects (≥1 month of age).

Final Market Image:

| Age [Months] | Body Weight [kg] | Daily dose | Number of tablets to be dispersed |
|---|---|---|---|
| ≥ 1 and < 6 | not applicable | 1.0 mg | 1×1.0 mg |
| ≥ 6 and < 24 | not applicable | 2.5 mg | 1×2.5 mg |
| ≥ 24 | ≥10 kg and < 15 kg | 3.5 mg | 1×1.0 mg & 1×2.5 mg |
| | ≥15 kg and < 25 kg | 5.0 mg | 2×2.5 mg |
| | ≥25 kg and < 50 kg | 7.5 mg | 3×2.5 mg |
| | ≥ 50 kg | 10.0 mg | 4×2.5 mg |

For subjects ≥ 2 y.o. the daily doses depend on the body weight category of the subjects and doses will be adjusted for change to body weight during the study as needed.

For subjects < 2 y.o., the daily doses depend on the age of the subject and will be adjusted during the study.

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| | Body weight or age for potential dose adjustment will be verified every 12 weeks at scheduled study visits.<br><br>In subjects ≥ 2 y.o., phosphodiesterase Type 5 (PDE-5) inhibitor is the only allowed PAH-specific background medication until disease progression.<br><br>In subjects < 2 y.o., oral/ inhaled prostanoid treatment are also allowed as PAH-specific background therapy in all study periods.<br><br>**Control arm / Standard of Care (SoC)**<br>SoC (including PAH non-specific treatment and/or up to two PAH-specific medications as per local practice) is the control group.<br><br>Children treated with a PDE-5 inhibitor and/or other PAH-specific treatment (such as an ERA or inhaled/oral prostanoids) at Baseline continue their medications. Additional PAH-specific therapy (excluding macitentan and IV/SC prostanoids) prescribed as SoC prior to randomization can be initiated.<br><br>Dose adjustments to reach the targeted dose or sequential introduction of combination therapy are allowed as prescribed by the investigator in Interactive Response Technology (IRT) prior to randomization. After randomization, change in a PAH-specific medication is allowed, if remaining within the same drug class. |
| CONCOMITANT THERAPY | **Mandatory concomitant therapy**<br>In both treatment arms female subjects of childbearing potential who are sexually active must use reliable contraceptive methods until EOS or until the last safety follow-up (FU) call (whichever occurs latest). If hormonal contraceptives are used those must be initiated at least 4 weeks before randomization.<br><br>For subjects who become sexually active any time after randomization and who are of childbearing potential, |

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| | contraceptive method(s) that are immediately effective must be applied.<br><br>**Allowed concomitant therapy**<br>Supportive PAH non-specific therapies (e.g., diuretics, anticoagulants, oxygen, calcium channel blockers) and changes to such medications are allowed during all study periods in both treatment arms. For IV diuretics and continuous oxygen therapy, refer also to 'PAH treatment escalation.'<br><br>Screening Period: Any PAH-specific therapy (excluding macitentan and IV./SC prostanoids) can be given or initiated as mono- or combination therapy with a maximum of two treatments.<br><br>Cohort of children < 2 y.o.: is allowed to use macitentan during Screening.<br><br>Core Period:<br>Macitentan group<br>Pre-Event SP: PDE-5 inhibitor treatment ongoing at randomization can continue.<br>Post-Event SP: Any PAH-specific medication (including IV/SC prostanoids), except ERA, can be administered in addition to macitentan.<br>SoC group<br>Pre-Event SP: Any PAH-specific treatment (other than macitentan and IV/SC prostanoids) as either mono- or double combination therapy identified as planned SoC before randomization can be administered.<br>Post-Event SP: Any PAH-specific medication (including IV/SC prostanoids) can be administered. Macitentan treatment will be offered after CEC confirms disease progression, if this is in the best interest of the subject per their investigator's judgment.<br><br>Single-arm Extension Period: |

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| | Any PAH-specific medication except an ERA can be administered in addition to macitentan.<br><br>Use of IV prostanoids for vasoreactivity testing is allowed in all study subjects and during all study periods.<br><br>**Forbidden concomitant therapy**<br>To avoid confounding effects, the following treatments are forbidden as specified:<br><br>• Use of any investigational drug is forbidden from 4 weeks before randomization/Visit 2 and up to EOS in all subjects.<br>• I.V./S.C. prostanoids are forbidden from 4 weeks before randomization/Visit 2 and during Pre-Event SP in all subjects (except if given for vasoreactivity testing).<br>• Use of macitentan is forbidden in all subjects ≥ 2 y.o. at any time before study entry. In the SoC group, macitentan is forbidden during the Pre-Event SP.<br>• In subjects ≥ 2 y.o. in the macitentan arm, the use of any PAH-specific background therapy other than PDE-5 inhibitor is forbidden during the Pre-Event SP.<br><br>Concomitant use of an ERA (e.g., bosentan, ambrisentan) with macitentan is forbidden during entire study duration.<br><br>Cohort of children < 2 y.o.: use of macitentan is allowed at any time before study entry and oral/inhaled prostanoids are allowed as PAH-specific background therapy.<br><br>To avoid drug-drug interactions with macitentan the following treatments are forbidden as specified:<br><br>• Strong inducers of CYP3A4 such as rifabutin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, and St. John's wort (hypericum perforatum) are forbidden from 4 weeks prior to and until randomization/ Visit 2 because the efficacy of macitentan could be reduced. After randomization/ Visit 2 these medications should be avoided as follows: in the macitentan arm until EOM. |

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| | in the SoC arm from 4 weeks before crossing over to macitentan and until EOM.<br>in the SAEP until EOS.<br>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.<br>• Systemic administration of strong inhibitors of CYP3A4 such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole is forbidden from 4 weeks prior to and until randomization/ Visit 2. After randomization/ Visit 2 systemic administration of these medications is forbidden as follows:<br>in the macitentan arm until EOM.<br>in the SoC arm from 4 weeks before crossing over to macitentan and until EOM.<br>in the SAEP until EOS.<br>• Systemic administration of moderate dual CYP3A4/CYP2C9 inhibitor such as fluconazole and amiodarone, or combination of a moderate CYP3A4 inhibitors (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (e.g., miconazole, piperine) is forbidden from 4 weeks prior to and until randomization/ Visit 2. After randomization/ Visit 2 systemic administration of these medications is forbidden as follows:<br>in the macitentan arm until EOM.<br>in the SoC arm from 4 weeks before crossing over to macitentan and until EOM.<br>in the SAEP until EOS.<br>In case such treatments are needed during study participation (except CYP3A4 inducers), macitentan treatment must be interrupted. To avoid any drug-drug interactions with SoC |

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| | treatments the investigator should consult respective medication label(s).<br><br>**PAH Treatment Escalation**<br>In the presence of PAH worsening, any PAH-specific treatment can be initiated per investigator's judgment. It is strongly recommended however to initiate PAH-specific medications, and/or continuous oxygen and/or IV diuretics, only in the presence of disease progression defined per protocol as per judgment of the investigator.<br><br>Subjects in the SoC group will be offered macitentan if the CEC confirms disease progression, and if this is considered in the best interest of the subject per their investigator's judgement. Subjects in the macitentan group will continue receiving macitentan after a CEC-confirmed disease progression event.<br><br>During the SAEP, PAH treatment can be escalated as per local practice. |
| ENDPOINTS | **Primary endpoint(s)**<br>In subjects ≥ 2 y.o. in the macitentan arm:<br><br>• Trough (pre-dose) plasma concentrations of macitentan and its active metabolite (ACT-132577) at Week 12 (steady-state conditions)<br><br>In subjects < 2 y.o. on macitentan:<br>• Trough concentrations of macitentan and its active metabolite (ACT-132577) at Week 4 (steady-state conditions)<br><br>PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight and age group in subjects ≥ 2 y.o. and < 2 y.o., respectively.<br><br>**Secondary efficacy endpoints**<br>The secondary endpoints are: |

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| | • Time to the first of the following CEC-confirmed disease progression events occurring between randomization/Visit 2 and EOCP:<br>o Death (all causes)<br>o Atrial septostomy or Potts' anastomosis, or registration on lung transplant list<br>o Hospitalization due to worsening PAH[§]<br>o Clinical worsening* of PAH defined as:<br>o Need for, or initiation of new PAH-specific therapy[#] or IV diuretics or continuous oxygen use AND at least one of the following:<br>▪ Worsening in WHO FC, or<br>▪ New occurrence or worsening of syncope (in frequency or severity as per medical judgment), or<br>▪ New occurrence or worsening of at least two PAH symptoms (i.e., shortness of breath/dyspnea, chest pain, cyanosis, dizziness/ near syncope, or fatigue), or<br>▪ New occurrence or worsening of signs of right heart failure not responding to oral diuretics.<br>[§] Excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (e.g., pneumonia).<br>* Worsening from baseline.<br>[#] E.g., ERA, PDE-5 inhibitor, prostanoids, prostacyclin receptor (IP receptor) agonist, soluble guanylate cyclase stimulator.<br>• Time to first CEC-confirmed hospitalization for PAH occurring between randomization/Visit 2 and EOCP.<br>• Time to CEC-confirmed death due to PAH occurring between randomization/Visit 2 and EOCP.<br>• Time to death (all causes) occurring between randomization/Visit 2 and Study Closure.<br>Following secondary endpoints are analyzed up to end of randomized macitentan or SoC + 7 days. Baseline is the last non-missing value observed before or on the day of randomization/ Visit 2. |

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| | • WHO FC status (I or II vs III or IV) at Week 24 .<br>• Percent of Baseline plasma NT-proBNP at Week 24.<br>• Change from baseline to Week 48 in mean daily time spent in moderate to vigorous physical activity as measured by accelerometry.<br>• Change from Baseline to Week 24 in tricuspid annular plane systolic excursion (TAPSE), and left ventricular eccentricity index measured by echocardiography (centrally assessed).<br>• Change from Baseline to Week 24 in Quality of Life as measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15).<br>**Exploratory endpoints**<br>• Panama FC status (I or II vs FC III or IV) at Week 24<br>• Change from Baseline up to Weeks 12, 24 and 48 in exercise capacity as measured by the 6MWT in children ≥ 6 years of age who are developmentally able to understand and perform the test.<br>Exploratory endpoints are analyzed up to end of randomized macitentan or SoC + 7 days. Further exploratory endpoints are described in the body text of the protocol.<br>**Safety endpoints**<br>Safety endpoints are assessed up to EOS and include:<br>• Adverse events (AEs)<br>• Serious adverse events (SAEs)<br>• AEs leading to premature discontinuation of macitentan or SoC<br>• AEs of special interest<br>• Marked laboratory abnormalities<br>• Change from Baseline in selected laboratory parameters to all timepoints of assessments<br>• Change from Baseline in vital signs (blood pressure, heart rate) to all timepoints of assessments |

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| | • Growth from Baseline to all timepoints of scheduled assessments<br>• Sexual maturation (Tanner stage) change from Baseline to all timepoints of scheduled assessments<br><br>Baseline is the last non-missing value observed before or on the day of randomization/ Visit 2.<br><br>**Other endpoints**<br>Other endpoints are described in the body text of the protocol. |
| ASSESSMENTS | Refer to the schedule of assessments in Table 1,Table 2 and Table 3. |
| STATISTICAL METHODOLOGY | **Analysis sets**<br>The Full Analysis Set 1 (FAS1, all randomized subjects ≥ 2 y.o. at randomization) is used for the analyses of all the efficacy and exploratory variables.<br><br>The Full Analysis Set 2 (FAS2, subjects < 2 y.o. at Visit 2) is used for the descriptive analyses of all efficacy and exploratory variables.<br><br>The Full Analysis Set 3 (FAS3, includes both FAS1 and FAS2) is used for the description of the study population at Baseline.<br><br>The Safety Set is used for the analyses of the safety variables.<br><br>The Screened Analysis Set is used for the description of subject disposition.<br><br>The PK Set 1 includes all subjects randomized to and treated with macitentan, for whom a PK blood sample at trough has been taken and who do not deviate from the protocol in a way that might affect the evaluation of the PK trough endpoints.<br><br>The PK Set 2 includes all subjects ≥ 2 y.o. randomized to and treated with macitentan or crossing over to macitentan and part of the PK substudy, who have evaluable PK profiles and who do not deviate from the protocol in a way that might affect the evaluation of the PK substudy endpoints. |

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| | The PK Set 3 includes all subjects < 2 y.o. treated with macitentan, for whom a PK blood sample has been taken and who do not deviate from the protocol in a way that might affect the evaluation of the PK endpoints.<br><br>**Primary variable**<br>In subjects who are ≥ 2 y.o. in the macitentan arm:<br><br>• Trough plasma concentrations of macitentan and its active metabolite ACT-132577 at Week 12 (steady-state conditions)<br><br>In subjects < 2 y.o.:<br><br>• Trough concentrations of macitentan and ACT-132577 at Week 4 (steady-state conditions)<br><br>PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight (≥ 2 y.o.) and age (< 2 y.o.) groups.<br><br>**Primary statistical analysis**<br>For macitentan and ACT-132577 trough concentration analysis, the PK Set 1 will be used.<br><br>PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight group. For children < 2 y.o. the analysis will be descriptive by age group.<br><br>Plasma and blood concentrations of macitentan and ACT-132577 per timepoint will be summarized by body weight groups and age groups in ≥ 2 y.o. and < 2 y.o., respectively, using arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and 2-sided 95% confidence interval (CI) of the mean.<br><br>**Secondary efficacy endpoints**<br><br>At Analysis 1 cutoff date, treatment effect estimates and 95% CLs will be provided for exploratory purposes only. No multiplicity adjustment will be applied. Analysis 2 cutoff date will be the primary analyses for these endpoints; p-values will |

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| | be provided in addition to treatment effect estimates and 95% CLs. Further details will be described in the statistical analysis plan (SAP). The analysis of the time to event variables will only be descriptive for subjects of the FAS2 (< 2 y.o. receiving macitentan) at Analysis 1 and 2 cutoff dates.<br><br>**Exploratory endpoints**<br>Due to the nature of these analyses, at Analysis 1 cutoff date, treatment effect estimates and 95% CLs will be provided for exploratory purposes only. At Analysis 2 cutoff date 2-sided p-values will be provided in addition to the treatment effect estimates and 95% CLs for exploratory purpose.<br><br>**Safety endpoints**<br>The number and percentage of subjects with at least one AE up to EOS, number and percentage of subjects with at least one SAE up to EOS, number and percentage of subjects with at least one AE leading to premature discontinuation of macitentan or SoC, and number and percentage of subjects with at least one AE up to EOS with fatal outcome will be tabulated by randomized treatment group and by:<br><br>• System organ class and individual preferred term within each system organ class, in descending order of incidence within the macitentan treatment group.<br>• Preferred term, in descending order of incidence in the macitentan treatment group.<br><br>Furthermore, for subjects exposed to macitentan, the number and percentage of subjects with at least one AE up to EOT + 30 days according to intensity, number and percentage of subjects with at least one AE up to EOT + 30 days according to relationship to macitentan, and number and percentage of subjects with at least one SAE up to EOT + 30 days according to relationship to macitentan will be tabulated by:<br><br>• System organ class and individual preferred term within each system organ class, in descending order of incidence within macitentan treatment group. |

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| | • Preferred term, in descending order of incidence in the macitentan treatment group.<br><br>Cohort of children < 2 y.o. will be summarized separately.<br><br>**Pharmacokinetic endpoints**<br>For PK profiles in subjects who are 2 years or older, the PK Set 2 will be used and PK Set 3 will be for PK assessment in children < 2 y.o.PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight group (≥ 2 y.o.) and age (< 2 y.o.) groups.<br><br>Plasma or blood concentrations of macitentan and ACT-132577 per timepoint will be summarized by body weight group or age group, respectively, using arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and 2-sided 95% CI of the mean.<br><br>Maximum plasma or blood concentration ($C_{max}$), the area under the plasma/ blood concentration-time curve during one dosing interval ($AUC_{\tau}$), and the time to reach maximum plasma/ blood concentration ($t_{max}$)* will be summarized with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, coefficient of variation inter-subject in %, and 95% CI of the arithmetic and geometric means.<br><br>* For $t_{max}$ the geometric mean and its 95% CI will not be calculated. |
| STUDY COMMITTEES | An **Independent Data Monitoring Committee (IDMC)** will review data at regular intervals according to the IDMC Charter. The IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety, tolerability and efficacy data obtained in the study and making appropriate recommendations based on the reported data.<br><br>An Independent Statistical Analysis Center (ISAC) will support the IDMC for their review and recommendation over the entire course of the study. |

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| | In addition, the ISAC will monitor, in collaboration with the IDMC, the number of disease progression events occurring over time, in order to make appropriate predictions for number of events anticipated by timepoint of Analysis 1 and Analysis 2.<br><br>A **Clinical Event Committee (CEC)**, an independent committee of PAH experts (including pediatricians), will review and adjudicate in a blinded fashion the secondary endpoints related to disease progression according to the CEC Charter. If there is any change to key data, as defined in the CEC Charter, or new key data become available after a first submission of a subject case has been submitted to the CEC, the CEC Coordinator re-submits the case for re-adjudication.<br><br>An independent **BCAC** will centrally review and confirm eligibility of subjects with co-incidental congenital heart disease before their randomization (before macitentan start for children <2 y.o.) as described in the BCAC Charter.<br><br>An **Independent Liver Safety Data Review Board (ILSDRB)**, a non-study-specific external expert committee of hepatologists, will receive cases of serious hepatic events of special interest from the Sponsor. This board provides ongoing assessment and advice regarding cases that may require further evaluation during the study. |
| PK SUBSTUDY | For up to 40 subjects ≥ 2 years of age receiving macitentan participation to the PK substudy is optional and will be controlled via IRT.<br><br>At steady-state conditions a PK profile will be collected over 24 hours from subjects ≥ 2 y.o. treated with macitentan. Collected PK data (both PK profiles and trough concentrations) will be regularly assessed using non-linear mixed effects PK modeling during the course of the study to confirm the appropriateness of the selected dosing regimen in subjects older than 2 years. A formal sample size calculation will determine the amount of PK data (full PK profile plus trough samples collected) required to ensure at least 80% power to |

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| | conclude that exposure in pediatric subjects is as targeted from the knowledge available from adults.<br><br>Modeling and simulation have been performed based on the PK data from pediatric subjects older than 2 years and adults to select the appropriate daily dose in subjects below 2 years of age. The modeling and PK data will be reported separately (i.e., not included in the Clinical Study Report). |

**Table 1: Visit and Assessment Schedule During Core Period for Subjects ≥ 2 y.o.**

| Periods | | SCREENING | CORE PERIOD | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VISITS | Number | 1 | 2 | 3 | 4, 5, 6, … | DP | CO | U1, U2, … | EOM | Safety FU | EOCP | Survival FU |
| | Name | Screening | Rando-mization | PK Substudy Visit[1] | Scheduled Visits | Disease Progression | Cross-over to macitentan[2] | Unscheduled Visits[3] | Premature End of macitentan | Safety Follow-up[4] | End of Core Period | Survival Follow-up[5] |
| | Time | ≤ 6 weeks before Randomization | Day 1 | At steady-state | Every 12 weeks (± 2 weeks) | Any day between Day 1 and EOS | Any day after CEC-confirmed DP and ≤ EOS | Any day between Day 1 and EOS | ≤ 1 week (+1 week) after last macitentan dose | 30 days (+ 1 week) after end of treatment or after EOS | Last visit before clinical cut-off date of Analysis 2 | At least yearly and until clinical cut-off date for Analysis 2 |
| **Informed consent/assent** | | X | - | - | - | - | Consent/ assent for Cross-over | - | - | - | Consent/ assent for SAEP | - |
| **Medical history incl. PAH diagnosis/ disease characteristics / demographics** | | X | - | - | - | - | Eligibility to take macitentan | - | - | - | Eligibility to take macitentan | - |
| **Previous/ concomitant therapy** | | X | X | X | X | X | X | X | X | - | X | PAH-specific medications |
| **PAH-related non-pharmacological interventions** | | X | X | X | X | X | X | X | X | - | X | - |
| **PAH signs/symptoms** | | X | X | X | X | X | X | X | X | - | X | - |
| **Functional Class[6]** | | X | X | - | X | X | X | X | X | - | X | - |

| Name | Screening | Rando-mization | PK Substudy Visit[1] | Scheduled Visits | Disease Progression | Cross-over to macitentan[2] | Unscheduled Visits[3] | Premature End of macitentan | Safety Follow-up[4] | End of Core Period | Survival Follow-up[5] |
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| **Subject narrative** | - | X | - | - | X | - | - | - | - | - | - |
| **Supportive data for DP[7]** | - | - | - | - | X | - | - | - | - | - | - |
| **NT-proBNP sampling** | - | X | - | X | X | X[8] | - | X | - | X | - |
| **Echocardio-graphy** | Local and Central | - | - | Visits 4, 5 (Central) | Local | - | - | - | - | - | - |
| **Physical activity[9]** | X | - | - | Visits 4, 5, 7 | - | - | - | - | - | - | - |
| **6MWT[10]** | X | X | | Visits 4, 5, 7 | X | - | | | | | |
| **Vital signs (BP, heart rate)** | X | X | X | X | X | X | - | X | - | X | - |
| **Weight and height** | X | X | Weight only | X | - | X | - | X | - | X | - |
| **Physical examination** | X | X | X | X | X | X | X | X | - | X | - |
| **Tanner stage** | X | - | - | Q24W | - | - | - | X | - | X | - |
| **Laboratory tests[11]** | X | X (if last test > 1 week) | X | X | - | X[12] | - | X | - | X | - |
| | | Hgb/hct, liver tests:Q4W (± 1 week) first 26 wks then Q12W[13] | | | - | Hgb/hct, liver tests Q4W for 26 wks | Re-test if applicable | X | - | X | - |
| **Pregnancy test in SOCBP** | serum | X[14] | Every 4 weeks (urine)[15] | | | | | | | | - |
| **Palatability of macitentan** | - | X | - | Visit 4 | - | - | - | - | - | - | - |

| Name | Screening | Rando-mization | PK Substudy Visit[1] | Scheduled Visits | Disease Progression | Cross-over to macitentan[2] | Unscheduled Visits[3] | Premature End of macitentan | Safety Follow-up[4] | End of Core Period | Survival Follow-up[5] |
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| **Quality of Life** | - | X | - | Visits 4, 5, 7 then Q48W | X | - | - | - | - | X | - |
| **PK sampling** | - | - | X[16] | Trough PK at Visit 4 | - | - | - | - | - | - | - |
| **Macitentan dispensing/ return[17]** | - | X[18] | - | X | - | X | - | X | - | X | - |
| **Document planned SoC in IRT** | X | X | - | - | - | - | - | - | - | - | - |
| **AEs/SAEs[19]** | X | X | X | X | X | X | X | X | X | X | Fatal SAE |
| **Vital Status** | - | - | - | - | - | - | - | - | - | - | X |

6MWT 6 minute walk test; AE adverse event; BP blood pressure; CEC Clinical Event Committee; CO cross over; DP disease progression; eCRF electronic case report form; EOM end of macitentan; EOCP end of core period; EOS end of study; ERA endothelin receptor antagonist; FU follow up; hct hematocrit; Hgb Hemoglobin; IRT Interactive Response Technology; NT proBNP N terminal pro brain natriuretic peptide; PAH pulmonary arterial hypertension; PK pharmacokinetics; Q12W every 12 weeks; Q24W every 24 weeks;Q48W every 48 weeks; SAE serious adverse event; SAEP single arm extension period; SoC standard of care; SOCBP subject of childbearing potential; WHO FC World Health Organization Functional Class.

1 The PK substudy visit will take place at steady state conditions (i.e., subject receives same dose of macitentan for ≥ 10 days).
2 Crossover visit only applies to subjects in the SoC group who have a CEC confirmed disease progression event.
3 Unscheduled visits are not mandated per study protocol but may be performed at any time during the study as per local practice. Such visits must at a minimum include the indicated assessments. Respective data are recorded in the eCRF. Laboratory re test due to abnormal hemoglobin or liver tests must be reported in the eCRF if performed.
4 Applicable for subjects who prematurely discontinue macitentan or SoC treatment, and to those subjects who do not enter the Extension study. End of standard of care will be declared if a planned PAH specific drug class is discontinued or if any additional PAH specific drug class is added or subject crosses over to macitentan. The Safety Follow up visit is performed by an investigator and can be done via telephone.
5 Applicable for subjects who prematurely discontinue regular study visits. Data are collected at least yearly and additionally within 6 weeks before the cutoff date for Analysis 1 and Analysis 2. Data can be obtained via visit, telephone or in writing (e.g., letter)

6 Both Panama FC and classical WHO FC are assessed. Panama FC is assessed in subjects until the age of 16 years.
7 Relevant data denoting disease progression are submitted to the CEC.
8 Only mandated for subjects eligible to start macitentan crossover treatment.
9 Data is collected in subjects ≥ 2 y.o. via accelerometer carried by the subject for 10  14 days.
10 6MWT in subjects ≥ 6 years of age who are able to understand and perform the test correctly. Only for subjects for whom 6MWT can be done at randomization.
11 Assessed at Central Laboratory. If data is missing, routine local laboratory data (if available) is recorded in the eCRF.
12 Only mandated for subjects eligible to start macitentan crossover treatment.
13 The investigator may decide to continue monthly liver tests via central laboratory. This is not mandated per protocol, but tests are mandatory every 12 weeks. In the SoC group monthly tests are only mandatory for subjects receiving an ERA for which the label instruction requests monthly tests. In other subjects in the SoC group those tests are done at the regular study visits (i.e., every 12 weeks).
14 Subjects of childbearing potential who are sexually active should be receiving at least 4 weeks of contraception before the urine pregnancy test at randomization. The pregnancy test is done locally.
15 Monthly pregnancy tests can be done at home under parental supervision. In this case the investigator will verify via phone that the test was done and will verify the results.
16 A PK profile is collected over a period of 24 hours (pre dose and then 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h post dose) in up to 40 subjects as part of the PK substudy.
17 Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
18 Parent(s)/caregiver(s) and subjects are instructed that macitentan should not be administered on days of study visits 3 (Day 14 PK) and 4 (Week 12) until instructed by site personnel.
19 All AEs and SAEs that occur after signing the Informed Consent Form and up to EOS or up to Safety FU (whichever is last) must be reported.

**Table 2: Visit and Assessment Schedule During Core Period for Cohort of Children < 2 y.o.**

| Periods | | SCREENING | CORE PERIOD | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VISITS** | **Number** | **1** | **2** | **WK4** | **WK8** | **4, 5, 6, …** | **DP** | **U1, U2, …** | **EOM** | **Safety FU** | **EOCP** | **Survival FU** |
| | **Name** | **Screening** | **Rando-mization** [20] | **Week 4** | **Week 8** | **Scheduled Visits** | **Disease Progression** | **Unscheduled Visits** [21] | **Premature End of macitentan** | **Safety Follow-up** [22] | **EOCP** | **Survival Follow-up** [23] |
| | **Time** | ≤ 6 weeks before Visit 2 | Day 1 | Between Day 21 and Day 35 (steady-state) | Between Day 49 and Day 63 (steady state) | Every 12 weeks (± 2 weeks) | Any day between Day 1 and EOS | Any day between Day 1 and EOS | ≤ 1 week (+1 week) after last macitentan dose | 30 days (+ 1 week) after end of treatment or after EOS | Last visit before clinical cut-off date of Analysis 2 | At least yearly and until clinical cut-off date of Analysis 2 |
| **Informed consent/assent** | | X | - | - | - | - | - | - | - | - | Consent/ assent for SAEP | - |
| **Medical history incl. PAH diagnosis/ disease characteristics / demographics** | | X | - | - | - | - | - | - | - | - | Eligibility to take macitentan | - |
| **Previous/ concomitant therapy** | | X | X | X | X | X | X | X | X | - | X | PAH-specific medications |
| **PAH-related non-pharmacological interventions** | | X | X | X | X | X | X | X | X | - | X | - |
| **PAH signs/symptoms** | | X | X | X | X | X | X | X | X | - | X | - |
| **Functional Class** [24] | | X | X | | - | X | X | X | X | - | X | - |
| **Subject narrative** | | - | X | - | | - | X | - | - | - | - | - |

| Name | Screening | Rando-mization [20] | Week 4 | Week 8 | Scheduled Visits | Disease Progression | Unscheduled Visits [21] | Premature End of macitentan | Safety Follow-up [22] | EOCP | Survival Follow-up [23] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Supportive data for DP** [25] | - | - | - | - | - | X | - | - | - | - | - |
| **NT-proBNP sampling-** | X | - | - | - | X | X | - | X | - | X | - |
| **Echocardiography** | Local and Central | - | - | - | Visits 4, 5 (central) | Local | - | - | - | - | - |
| **Vital Signs (BP, heart rate)** | X | X | X | X | X | X | - | X | - | X | - |
| **Weight and length/height** | X | X | Weight | Weight | X | - | - | X | - | X | - |
| **Physical examination** | X | X | X | X | X | X | X | X | - | X | - |
| **Laboratory tests** [26] | X | X | Hgb/hct, liver tests | Hgb/hct, liver tests | X | - | Re-test if applicable | X | - | X | - |
| | | Hgb/hct every 4 weeks until Week 24<br>Liver tests every 4 weeks until Week 48 [27] | | | | | | | | | |
| **Palatability of macitentan** | - | X | - | - | Visit 4 | - | - | - | - | - | - |
| **PK sampling** | - | X [28] | X | X | - | - | - | - | - | - | - |
| **Macitentan dispensing/return** [29] | | X [30] | - | - | X | - | - | X | - | X | - |
| **AEs/SAEs** [31] | X | X | X | X | X | X | X | X | X | X | Fatal SAE |
| **Vital Status** | - | - | - | - | - | - | - | - | - | - | X |

20 This cohort will not be randomized but will directly enter the macitentan arm. In order to keep the study set up as simple as possible the Visit 2 is called "Randomization" for all subjects.

21 Unscheduled visits are not mandated per study protocol but may be performed at any time during the study as per local practice. Such visits must at a minimum include the indicated assessments. Respective data are recorded in the eCRF. Laboratory re test due to abnormal hemoglobin or liver tests must be reported in the eCRF if performed.

22 Applicable for subjects who prematurely discontinue macitentan, and to those subjects who do not enter the Extension study. The Safety Follow up Visit is performed by an investigator and can be done via telephone.

23 Applicable for subjects who prematurely discontinue regular study visits. Data are collected at least yearly and additionally within 6 weeks before the cutoff date for Analysis 1 and Analysis 2. Data can be obtained via visit, telephone or in writing (e.g., letter).
24 Both Panama FC and classical WHO FC are assessed.
25 Relevant data denoting disease progression are submitted to the CEC.
26 Assessed at Central Laboratory. If data is missing, routine local laboratory data (if available) is recorded in the eCRF.
27 Use of local laboratory is allowed, if normal range for applicable age group is available. Monthly tests will continue until 48 weeks after the first dose of macitentan study treatment even if this falls into the Extension Period (refer to **Table 3**).
28 PK samples will be drawn at 2h, 5h, and 24h after the first dose.
29 Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
30 Parent(s)/caregiver(s) and subjects are instructed that macitentan should not be administered on days of study visits Week 4 and Week 8 until instructed by site personnel.
31 All AEs and SAEs that occur after signing the Informed Consent Form and up to EOS or up to Safety FU (whichever is last) must be reported.

**Table 3: Visit and Assessment Schedule During Single-arm Extension Period**

| **Periods** | | **SINGLE-ARM EXTENSION PERIOD** | | | | |
|---|---|---|---|---|---|---|
| **VISITS** | **Number** | **EOCP** | **ML** | **EV** | **EOS** | **Safety FU** |
| | **Name** | **End of Core Period** | **Extra Lab Tests** | **Extension Visits** | **End of Study** | **Safety Follow-up** |
| | **Time** | last visit before clinical cut-off date of Analysis 2 | Every 4 weeks (± 1week) for subjects ≥ 2y.o. until 24 weeks after first dose of IMP for subjects <2y.o. until 48 weeks after first dose of IMP | Every 12 weeks (± 2 weeks) | ≤ 12 weeks after SC announcement | 30 days (+ 1 week) after end of treatment or after EOS |
| **Eligibility to start/continue macitentan including informed consent/assent** | | X | - | - | - | - |
| **Concomitant therapy** | | X | - | X | X | - |
| **Efficacy assessments as indicated in Table 1** | | X | - | - | - | - |
| **Vital signs (BP, heart rate)** | | X | - | X | X | - |
| **Weight and height/length** | | X | - | X | X | - |
| **Physical examination** (not recorded in eCRF after EOCP) | | X | - | X | X | - |
| **Tanner stage** is assessed in girls ≥ 8 y.o. and in boys ≥ 9 y.o. until full maturation (self-assessment by family is allowed) | | X | - | X | X | - |
| **Childbearing Potential (CBP)** is assessed as per local practice in female subjects until CBP is confirmed | | X | - | X | X | - |
| **Laboratory tests** are centrally assessed (if data are missing, routine local lab data will be recorded in the eCRF, if available, including respective normal range values). | | X | - | X | X | - |

| Name | End of Core Period | Extra Lab Tests | Extension Visits | End of Study | Safety Follow-up |
|---|---|---|---|---|---|
| **Liver tests and hemoglobin/ hematocrit** If monthly tests are done at local laboratory, the investigator must call the local hospital to request and review the results. Hemoglobin/ hematocrit will be assessed monthly until 24 weeks after first IMP dose in all age groups and then quarterly. For liver tests switch from monthly to quarterly testing depends on age group. | X | X | X | X | - |
| **Urine pregnancy test in SOCBP** Subjects of childbearing potential who are sexually active should be counselled for contraception. The monthly pregnancy tests can be done locally under supervision of parents (in subjects not yet of legal age). The investigator (or delegate) contacts the family every month to document the date/result of monthly urine pregnancy test. | X | Monthly | Monthly | X | X |
| **Macitentan dispensing/return** Scheduled study medication dispensing/return procedures may be adapted according to the site practice. | X | - | X | Return | - |
| **AEs/SAEs** All AEs and SAEs that occur up to EOS or up to Safety FU (whichever is last) must be reported. For subjects transitioning to PTA or LTE study after TOMORROW SAEP the Safety FU call will be waived since they will be monitored in the respective PTA/LTE study. | X | - | X | X | X |

AE adverse event; BP blood pressure; CBP childbearing potential; eCRF electronic case report form; EOS end of study; EV extension visits; FU follow up; IMP investigational medicinal product; LTE long term extension; ML monthly labs; PTA post trial access; SAE serious adverse event; SAEP single arm extension period; SC study closure; SOCBP subject of childbearing potential

# PROTOCOL

# 1 BACKGROUND

## 1.1 Indication

Treatment of pulmonary arterial hypertension (PAH) in children.

### 1.1.1 Definition and Diagnosis

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 [Widlitz 2003, 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 (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 Wood units (WU) x $m^2$ [Ivy 2013, Abman 2015, Hansmann 2016].

PVRi [WU x $m^2$] mPAP [mm Hg] - PAWP [mm Hg] / Cardiac index [(L/min) / $m^2$]

Cardiac index [(L/min) / $m^2$] Cardiac output [L/min]/ body surface area [$m^2$]

PAH diagnosis can be confirmed only if elevated left heart pressures are excluded as a reason for pulmonary hypertension. PAWP is used for this purpose as a surrogate of a directly measured pressure in the left atrium [Galiè 2015]. In the absence of mitral stenosis, left ventricular end diastolic pressure (LVEDP) can also be used as an alternative surrogate for left atrial pressure (LAP) [Grignola 2011, Takala 2003].

### 1.1.2 Classification

According to the revised clinical classification of pulmonary hypertension [Simonneau 2013] PAH comprises: idiopathic PAH (iPAH); heritable PAH (hPAH); drug-and toxin-induced PAH; and PAH associated with connective tissue diseases (PAH-aCTD), HIV infection, portal hypertension, congenital heart diseases (CHD), schistosomiasis; it also includes the subcategories pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis as well as persistent pulmonary hypertension of the newborn [Ivy 2013].

This protocol addresses iPAH, hPAH, and PAH associated with CHD which account for the majority of pediatric PAH patients [refer to Section 1.1.3]. PAH associated with HIV, PAH associated with CTD, as well as drug or toxin-induced PAH are also included in this trial even though they represent only a minor proportion of the pediatric PAH population [D-16.012].

Within the subgroup of PAH associated with CHD, the protocol excludes patients with Eisenmenger syndrome as well as patients with open left-to-right shunts. In those patients, there is not sufficient adult data available to support efficacy of macitentan.

### 1.1.3 Epidemiology

Knowledge about incidence and prevalence of PAH in children is limited to a few national registries. A retrospective, nationwide registry-based study performed in the Netherlands during 1991-2005 revealed an annual incidence and point prevalence of 0.7 and 4.4 cases per million children for iPAH, and 2.2 and 15.6 cases per million children for PAH associated with CHD, respectively [van Loon 2011]. In France in 2005, the estimated annual prevalence per million children was 2.2 cases of iPAH [Fraisse 2010]. Data from the UK National Pulmonary Hypertension Service between 2001 and 2007 showed that the incidence of iPAH was 0.48 cases per million children per year, and the prevalence 2.1 cases per million children [Moledina 2010].

In the majority of pediatric patients, PAH presents as iPAH or PAH associated with CHD [Ivy 2013]. Data from various PAH pediatric registries have shown that iPAH accounts for 35% to 60% of cases in children, whereas CHD is also a common cause of PAH accounting for 24% to 52% of pediatric patients (UK PH service [Moledina 2010]; the French PH registry [Fraisse 2010]; the Netherlands PH registry [van Loon 2011]; the TOPP registry [Berger 2012]; the US REVEAL registry [Barst 2012a]).

Diagnosis of PAH in children occurs at all ages and with an almost equal gender distribution. These results are based on a systematic review of four prospective observational registries [D-16.012].

### 1.1.4 Current Treatment and Unmet Clinical Need

At the time the study was designed, there was no PAH-specific therapy approved globally for use in children. In Europe, sildenafil and bosentan were approved for pediatric use. Bosentan was also approved for pediatric use in Japan. No PAH-specific therapies were approved for children in the US. In the meantime, bosentan received approval for pediatric use in some countries, such as China and the US.

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 5$^{th}$ World Symposium for PH [Ivy 2013]. Results from different cohorts suggest that survival has

improved in pediatric patients with the use of these therapies [Haworth 2009, Barst 2012a, Moledina 2010, van Loon 2010, Zijlstra 2014]. However, treatment remains unsatisfactory, with 5-year survival rates ranging from 71% to 75% [Ivy 2013].

Hence 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.

## 1.2 Study Treatment(s)

### 1.2.1 Macitentan

Macitentan (Opsumit®; macitentan 10 mg film-coated tablets) monotherapy or in combination is indicated for the long-term treatment of PAH in adult patients of WHO Functional Class (FC) II to III to delay disease progression. Macitentan has been approved for PAH in multiple countries worldwide including the US, the European Economic Area (EEA), Switzerland, Canada, Australia, and Japan.

Macitentan has been selected for further clinical development in pediatrics due to its long-term effectiveness and good safety profile in adult PAH.

#### 1.2.1.1 *Mechanism of Action*

Macitentan is an orally active, nonpeptide, potent dual endothelin (ET) $ET_A$ and $ET_B$ receptor antagonist (ERA).

The endothelin system comprises a family of proteins originally described for their vasoconstrictive activity [Levin 1995, Masaki 2000]. ET-1, a 21-amino acid peptide produced by endothelial and other cells, is considered one of the most potent vasoconstrictors known. Additionally, endothelins such as ET-1 and their receptors act as paracrine and autocrine tissue factors to regulate biological processes such as tissue remodeling and repair, smooth muscle cell proliferation and inflammation [Teder 2000, Clozel 2003].

ET-1 is over-expressed in several forms of pulmonary vascular disease. It is likely a major player in the vasodilator and vasoconstrictor imbalance, as well as in the abnormal pulmonary vascular remodeling present in the development and progression of pulmonary hypertension of various etiologies [Stewart 1991, Giaid 1993]. Plasma levels of ET-1 correlate with pulmonary hemodynamics [Giaid 1993], PAH severity and prognosis [Rubens 2001].

Macitentan showed a dose-dependent efficacy similar to that observed with bosentan (Tracleer®, the first ERA registered for the treatment of patients with PAH) in nonclinical models of hypertension and PAH, but macitentan was approximately 10 times more potent than bosentan.

#### 1.2.1.2 *Pharmacokinetics and Metabolism*

For details provided in this section and further information refer to the Investigator's Brochure (IB) ACT-064922 [Macitentan IB].

Macitentan has a pharmacologically active metabolite, aprocitentan (ACT-132577), 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 ACT-132577). After multiple-dose administration steady-state conditions of macitentan are obtained after 3 days (and 7 days for ACT-132577). Macitentan accumulates only minimally (about 1.5-fold), whereas the active metabolite ACT-132577 accumulates substantially (about 8.5-fold). For plasma concentrations and other pharmacokinetic (PK) parameters measured in Phase 1 studies, refer to the [Macitentan IB].

Bioavailability of macitentan and exposure to ACT-132577 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 ACT-132577.

Macitentan clearance is mediated by several human P450 enzymes including CYP3A4 and CYP2C9 and is mainly eliminated via the urine (49.7% ± 3.9%).

ACT-132577 is approximately 5-fold less potent than macitentan *in vitro*. However, in humans systemic exposure to ACT-132577 is about 3-fold higher as compared to macitentan, and ACT-132577 contributes to the overall pharmacological effect. Formation of ACT-132577 is mainly catalyzed by CYP3A4. At the maximum dose of 10 mg planned in this clinical trial, macitentan and ACT-132577 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 ACT-132577. Conversely, macitentan's effect on sildenafil exposure is modest and can also be ignored.

In the presence of strong inhibitors of CYP3A4 (e.g., ketoconazole) and moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., 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.

#### 1.2.1.3 *Efficacy in Adult Patients With Pulmonary Arterial Hypertension*

In SERAPHIN (AC-055-302), a multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase 3 study in adult patients with symptomatic PAH, 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 event with a hazard ratio (HR) of 0.547 versus placebo (97.5% confidence limits [CL] 0.392-0.762, log-rank $p < 0.0001$). The HR in the macitentan 3 mg group versus placebo was 0.704 (97.5% CL 0.516-0.960, log-rank 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, log-rank $p < 0.0001$). The respective HR in the macitentan 3 mg group versus placebo was 0.669 (97.5% CL 0.462-0.970, log-rank 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].

#### 1.2.1.4 *Nonclinical Safety Data*

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

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 [D-12.346], corresponding to 1.7-fold the human therapeutic exposure.

Available data indicate that nonclinical pharmacology, PK and available toxicity data support a pediatric development program and sNDA.

#### 1.2.1.5 *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 (i.e., 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 (i.e., 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] / aspartate aminotransferase [AST] > 3 × upper limit of normal range [ULN] was 3.4% on macitentan 10 mg and 4.5% on placebo, ALT/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 leukocyte count from Baseline of $0.7\times10^9$ /L versus no change in placebo-treated patients, and with a decrease in mean platelet count of $17\times10^9$ /L, versus a mean decrease of $11\times10^9$ /L in placebo-treated patients.

Macitentan doses of 150 mg once daily (o.d.) or higher (maximum 300 mg o.d.), generating exposures 6-10 times higher than those observed with 10 mg o.d., have been used over several months in combination with temozolomide in patients with glioblastoma [D-16.563]. 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 o.d. doses.

During the post-marketing 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 Investigator's Brochure [Macitentan IB].

### 1.2.2 Benefit-risk Assessment for Participation in This Clinical Trial

**Macitentan Group**

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. 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.

To support the use of macitentan in the pediatric population in children with PAH (TOMORROW, AC-055-312), a population PK model was developed to establish macitentan doses with the aim of achieving similar systemic exposures to those observed in adults with PAH, treated with macitentan 10 mg o.d. doses. Exposures for children ≥ 2 to < 18 years of age were predicted based on allometric scaling of an adult population PK macitentan model, derived using PK profiles obtained in patients with PAH in a PK substudy of the SERAPHIN open-label extension study. To cover the age range ≥ 2 to < 18 years with associated body weights (and volumes of distribution, i.e., blood), an optimization approach was used to determine the dosing for specific body weight ranges. Thereafter, simulations were performed to anticipate the distribution of exposure for the selected dosing strategy in relation to the adult exposure. The selected doses and their expected exposures in children are aimed at limiting under-dosing and insufficient therapeutic effect.

The data used to develop the macitentan adult population PK model consisted of plasma concentration samples collected over a 24-hour period at steady-state from 20 patients with PAH who participated in the SERAPHIN PK substudy (AC-055-303). This adult population PK model for macitentan was updated through allometric scaling. Age factors were not included in the model update as the metabolic pathways relevant for macitentan,

i.e., primarily cytochrome P450 3A4 (CYP3A4), are fully mature by 2 years of age [Johnson 2006].

The proposed macitentan dosing regimen to be used in pediatric subjects < 2 years old (y.o.) is as follows: 1 mg macitentan for subjects in the age range from 1 to < 6 months; and 2.5 mg macitentan for subjects in the age range from 6 months to < 2 y.o.

The dosing regimen in pediatric subjects < 2 y.o. was proposed based on a population PK modeling complemented with physiologically-based PK (PBPK) approach. A PK model previously developed in adults was updated with the data from pediatric subjects ≥ 2 y.o. The PK model was further incorporated with time course functions describing the development of cytochrome P450 (CYP) enzymes to account for the development of the elimination pathways in pediatric population < 2 y.o. (maturation functions). Simulations with different doses were performed to establish the appropriate dosing regimens to provide the predefined target systemic exposure range (i.e. $AUC_{ss}$) in subjects < 2 y.o. similar to those observed in adult subjects receiving the 10mg once daily clinical dose.

Ongoing review of safety data in pediatric population (off-label use) as part of the periodic safety update reports, did not raise any new safety concern including the population <24 months of age. In the TOMORROW population currently enrolled (i.e., ≥ 2 y.o.) did not reveal any new safety concern, either. There is no need for additional safety monitoring in children < 2 y.o. as compared to the safety monitoring done in children ≥ 2 y.o. As described in Section 10.1.1 investigators will instruct parents/ care givers of study subjects on how to report specific and unspecific symptoms (including vomiting, diarrhea, sleepiness, change in pattern of crying, etc.) in order to reduce the risk for under- or mis-reporting.

Taking into account the following factors, it is justified to include pediatric participants ≥ 1 month to < 18 years of age: no new safety concern from the currently enrolled population (i.e., ≥ 2 y.o.) in TOMORROW study, no new safety concern coming from the periodic safety reports in the population < 24 months, the lack of organ-specific toxicity or specific developmental concerns in juvenile animals; the safety profile corresponding to that of adult patients in adolescents on 10 mg doses showing no indication of different or more severe AEs in earlier studies and post-marketing; and the good tolerance for high doses and exposures of macitentan in adult patients with glioblastoma.

Macitentan is approved for treatment in adult PAH as a 10 mg o.d. dose based on a favorable benefit-risk ratio [see Sections 1.2.1.3 and 1.2.1.5 on efficacy and safety in adults]. 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 receiving a 10 mg dose, will also result in a favorable benefit-risk ratio.

**Comparator Group**

In the comparator group, subjects will receive best available care which may include an ERA (other than macitentan). Thus subjects will not be deprived of any treatment.

Additional Benefits and Safety Measures:

Subjects in both treatment groups will receive additional attention by being in a clinical trial including close monitoring every 12 weeks at a PAH expert center. In addition, if disease progresses, treatment can be escalated by the investigator immediately and without any restrictions, as per best local practice. Macitentan treatment will be offered to subjects in the SoC group after a CEC-confirmed disease progression event, if this is considered in their best interests per their investigator's judgment.

It is the investigator's responsibility to monitor the risk-benefit ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual subject level, and to discontinue study treatment or the study procedures if, on balance, he/she believes that continuation would be detrimental to the subjects' well-being.

Safety surveillance for patients participating in study AC-055-312 will additionally be ensured by an independent data safety monitoring committee (IDMC) which will periodically review unblinded safety and efficacy data [see Section 3.4].

### 1.2.3 Standard of Care

Although clinical studies have been performed in children with PAH (e.g., 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.

As per recent guidelines children with negative acute vasoreactivity response should be treated with an ERA or a phosphodiesterase Type 5 (PDE-5) inhibitor. If despite such treatment there is PAH deterioration, combination therapy should be given which can also include inhaled prostanoids. In children who are at higher risk of death (e.g., signs/symptoms of right heart failure, progression of PAH symptoms and/or WHO FC, syncope) it is strongly advised to initiate intravenous (IV) or subcutaneous (SC) prostanoids [Ivy 2013, Galiè 2015, Abman 2015].

#### 1.2.3.1 *Endothelin Receptor Antagonists*

ET-1 is over-expressed in several forms of pulmonary vascular disease. The mechanism of action of ERAs is described in Section 1.2.1.1.

Bosentan has been studied in children with PAH in five prospective, open-label trials: BREATHE-3, FUTURE 1, 2, 3 and 3 extension study [refer to Table 4].

## Table 4: Clinical Trials Studying Bosentan in Pediatric PAH

| Study | Study Objectives | Design | Study Population | Sample enrolled (n) | Treatment dose/ duration | Exploratory Efficacy Results |
|---|---|---|---|---|---|---|
| **BREATHE-3** [B-02.003] | PK, tolerability, safety of adult formulation | Prospective, multicenter, OL, non-controlled, parallel group, single- and multiple-dose | **Age:** 3-15 years<br>**Etiology:** primary PAH or aPAH-CHD<br>**Severity:** WHO FC II/III | 19 | **Dose:** ~2 mg/kg b.i.d.<br>> 40 kg: 125 mg b.i.d.<br>> 20-40 kg: 62.5 mg b.i.d.<br>10-20 kg: 31.25 mg b.i.d.<br>**Median Exposure:** 23.9 weeks | Mean changes from Baseline in hemodynamic variables:<br>**mPAP:** −8 mm Hg ($p < 0.01$),<br>**PVRi:** −300 dyn×sec×$m^2$/$cm^5$ ($p < 0.05$),<br>**CO:** +0.61 L/min ($p < 0.05$) |
| **FUTURE 1** [D-07.041] and its extension study **FUTURE 2** [D-12.790] | PK, safety, tolerability, efficacy of pediatric formulation | Prospective, multicenter, OL, single-arm, non-controlled | **Age:** 2-11 years<br>**Etiology:** iPAH, hPAH<br>**Severity:** WHO FC II/III | 36<br>(Extension study: 33) | **Dose:** 2 to 4 mg/kg b.i.d.<br>**Median Exposure:** 120 weeks (8-258 weeks) | **Disease progression** (death, transplantation, hospitalization for PAH worsening, new PAH therapy or new/worsening RHF): KM event-free estimates at Month 12 was 65.8% (95% CL: 47.7, 78.9%), at Month 24 was 56.2% (95% CL: 38.0, 71.0%), at Month 36 was 51.9% (95% CL: 33.4, 67.5%). |
| **FUTURE 3** and its extension study [D-13.335]<br>[D-14.491] | PK, tolerability, safety and efficacy of pediatric formulation | Prospective, multicenter, OL, randomized, multiple-dose | **Age:** 3 months-11 years<br>**Etiology:** iPAH/hPAH, aPAH-CHD (including Eisenmenger)<br>**Severity:** WHO FC I-III | 64<br>(Extension study: 58) | **Dose:** 2 mg/kg b.i.d. vs 2 mg/kg t.i.d.<br>**Median Exposure:** 72 weeks (0.4-90 weeks) | **WHO FC:** worsening from Baseline<br>At Month 12: 10.9% (12.1% in b.i.d., 9.7% in t.i.d.)<br>At Month 18: 12.5% (15.2% in b.i.d., 9.7% in t.i.d.)<br>**Disease progression** (death, lung transplant, hospitalization for PAH worsening, new PAH therapy or new/worsening RHF): KM event-free estimate at Month 12 was 81.4% (95% CL: 69.0, 89.3%)and at Month 18 was 74.1% (95% CL: 60.8, 83.6%)%). |

aPAH CHD PAH associated with congenital heart disease, b.i.d. twice a day, CO Cardiac Output, CL confidence limits, hPAH heritable PAH, iPAH idiopathic PAH, KM Kaplan Meier, mPAP mean pulmonary artery pressure, OL open label, PAH pulmonary arterial hypertension; PK pharmacokinetics, PVRi pulmonary vascular resistance index, RHF right heart failure, t.i.d. three times a day; WHO FC World Health Organization Functional Class. Sources [B 02.003; D 07.041; D 12.790; D 13.335; D 14.491].

For ambrisentan, another ERA, only limited data are available in children. In a retrospective cohort study, effects of ambrisentan were studied in 38 patients (aged 2 to 18 years). After a median treatment duration of 21 months there was a significant improvement in mPAP as compared to patients on alternative PAH-specific treatment. There was no effect on other hemodynamic variables (such as cardiac index, PVR index [PVRi]) [Takatsuki 2013a].

#### 1.2.3.2 *Phosphodiesterase-5 Inhibitors*

PDE-5 inhibitors prevent enzymatic degradation of cyclic guanine monophosphate and thereby lead to vasodilation. In addition they have some antiproliferative effects [MacKenzie 2015].

The effect of sildenafil was assessed in STARTS-1, a multicenter, randomized, double-blind, placebo-controlled dose-ranging study in treatment-naïve children with PAH (aged 1 to 17 years). Patients were randomized to either receive low-dose (n 42), medium-dose (n 55), high dose (n 77) sildenafil or placebo (n 60), see Table 5. After 16 weeks of treatment exercise capacity as measured by cardiopulmonary exercise testing (peak oxygen consumption, i.e., $PVO_2$) did not meet the primary endpoint (p 0.056). However, $PVO_2$ improved in the medium and high dose groups compared to placebo. In addition, there was improvement in mPAP and PVRi in the medium- and high dose sildenafil groups as compared to placebo [Barst 2012b]. Long-term treatment with sildenafil was assessed in the extension study, STARTS-2. Kaplan-Meier estimates for survival at 3 years were 93% for the low-dose, 91% for the medium-dose, and 87% for the high dose group [Barst 2014]. The EMA approved use of sildenafil in children with PAH but warned against use of the high dose. Sildenafil is not approved for pediatric use in the US nor is it recommended by the FDA for use in children [Revatio® USPI] and can only be considered for prescription on an individual basis.

**Table 5: Sildenafil Doses Administered 3 Times Daily in STARTS-1**

| | **Sildenafil dose [mg]** | | |
|---|---|---|---|
| Body weight [kg] | Low | Medium | High |
| ≥ 8 to 20 | Not applicable | 10 | 20 |
| > 20 to 45 | 10 | 20 | 40 |
| > 45 | 10 | 40 | 80 |

Derived from [Barst 2012b].

For tadalafil, retrospective data in 33 PAH patients (aged 4 to 18 years) have been published. In 4 patients tadalafil was given as initial therapy, in 29 patients sildenafil

treatment was switched to tadalafil mainly to allow once daily dosing. In 14 of those patients a repeat catheterization was performed and showed statistically significant improvement in mPAP and PVRi [Takatsuki 2012].

For vardenafil, there are no pediatric data. In treatment-naïve adults with PAH vardenafil increased exercise capacity, 6-minute walk distance (6MWD), and reduced clinical worsening as compared to placebo [Wardle 2013, Jing 2011].

#### 1.2.3.3 *Prostanoids*

Prostacyclin, an endogenous prostaglandin primarily produced by endothelial cells, is a potent inducer of vasodilation. In addition, it inhibits platelet aggregation and appears to have both cytoprotective and antiproliferative activities. In patients with PAH prostacyclin synthesis is reduced. Administration of prostacyclin or analogs can improve PAH symptoms, exercise capacity and hemodynamics [Galiè 2013].

In a cohort of 22 PAH patients (aged 4.5 to 17.7 years) inhaled iloprost lowered mPAP and caused sustained functional improvement. The need for 6 to 9 inhalations daily negatively impacting compliance and side effects such as bronchoconstriction may however limit chronic treatment in children [Ivy 2008].

A retrospective analysis performed in 29 PAH patients (aged 3.2 to 19 years) indicated that inhaled treprostinil as add-on to PAH-specific background therapy was associated with improved exercise capacity (6MWD and $PVO_2$) and WHO FC [Krishnan 2012]. The efficacy of IV and SC treprostinil seems to be comparable to the one of epoprostenol. This is based on a retrospective cohort of 77 patients with PAH (aged 0.04 to 13.3 years) evaluating hemodynamics and long-term transplant-free survival in patients receiving either of these medications [Siehr 2013]. Subcutaneous administration of treprostinil is however often painful and difficult to tolerate. In adults infusion site pain was reported in 92% of patients and 23% of patients discontinued treatment because of site pain and/or reaction [Barst 2006].

Retrospective data of using IV epoprostenol in children with severe PAH (WHO FC III/IV) suggest improvement in survival, WHO FC, and exercise capacity. In this retrospective cohort of 39 patients (aged 4 months to 17 years) IV epoprostenol was initiated if the children failed to appropriately respond to oral PAH-specific therapy or were severely symptomatic. Epoprostenol alone was insufficient to maintain clinical improvement in 14 children who needed additional treatment with either bosentan or sildenafil. Complications related to IV administration included infections and leaking lines [Lammers 2007].

## 1.3 Purpose and Rationale of the Study

The purpose of the study is to establish the PK, safety and efficacy of macitentan in children with PAH treated with a dispersible formulation using a clinical composite primary

endpoint and targeting a similar exposure as seen in adults with macitentan 10 mg [refer to Section 1.2.1.3].

The overall rationale is based on the positive Phase 3 study of macitentan in adults with PAH (AC-055-302) which showed significant clinical benefit and a good overall safety profile [refer to Sections 1.2.1.3 and 1.2.1.5].

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of the study is to evaluate the PK of macitentan in children with PAH.

## 2.2 Secondary Objectives

To assess safety and tolerability of macitentan in children with PAH.

To assess efficacy of macitentan in children with PAH.

# 3 OVERALL STUDY DESIGN AND PLAN

## 3.1 Study Design

This is a prospective, multicenter, open-label, randomized, controlled, parallel group, Phase 3 study with an open-label single-arm extension period to evaluate PK, safety and efficacy of macitentan in children with PAH.

Children < 2 y.o. will be assigned as a cohort to the macitentan group without randomization.

Approximately 200 subjects and no more than 300 subjects will be enrolled in this study based on current feasibility. Subjects ≥ 2 y.o. at Visit 2 will be randomized in a 1:1 ratio to either receive macitentan or continue SoC. Randomization is stratified by ongoing/planned ERA treatment at randomization (yes vs no) and by WHO FC at randomization (FC I/II vs FC III). The proportion of subjects with ERA treatment, as a component of the planned SoC**,** is limited to a maximum of 40% of the overall number of subjects randomized.

Cohort of children < 2 y.o. will not be randomized but will enter directly into the macitentan arm. The ERA cap does not apply to this cohort.

In consideration of the different requirements from Health Authorities, two important milestones (i.e., fourth quarter of 2022 (Analysis 1), and first quarter of 2024 (Analysis 2), respectively) will trigger the analysis timepoints.

There will be three time points of study analysis:

- Analysis 1 of Core Period: with cutoff date in the fourth quarter of 2022

- Analysis 2 of Core Period: with cutoff date in the first quarter of 2024
- Analysis 3 final analyses including the core and single-arm extension periods.

The sponsor will determine the cutoff date for the first two analyses three months prior to this date and will document the decision accordingly in the Trial Master File.

The cohort < 2 y.o. may be analyzed at additional timepoints in order to allow ongoing evaluation of benefit-risk in this vulnerable population.

Study duration for each individual subject will be based on their time of enrollment. All subjects are planned to remain in the study until the database lock in 2024 (Analysis 2). Thereafter, if it is considered in the best interest of the subject, continuation in the open-label single-arm extension period with macitentan will be offered.

The study will be conducted at approximately 90 sites in about 30 countries. Sites with no screening activities or subject enrollment may be replaced.

The study consists of the following periods:

**Screening Period:** Starts from signed informed consent and ends with randomization or confirmation of screening failure (up to 6 weeks after signed informed consent).

Cohort of children < 2 y.o.: The screening period ends with confirmation of eligibility (i.e., age at Visit 2 is less than 2 years) and assignment of macitentan kit at Visit 2, or with screening failure.

**Core Period:** Commences with Visit 2 and continues until the End of Core Period (EOCP) visit.

Pre-Event Study Phase (Pre-Event SP): Starts from Visit 2 until disease progression event confirmed by the CEC or until EOCP visit, whichever comes first.

Post-Event Study Phase (Post-Event SP): Begins with CEC-confirmed disease progression event and continues until EOCP visit. During Post-Event SP PAH-specific background treatment may be escalated in both treatment arms as per local practice. Any additional treatment, including IV or SC prostanoids may be used in both treatment arms. Subjects in the macitentan arm can continue receiving macitentan. Subjects in the SoC arm are offered to cross-over to macitentan treatment, if this is in their best interests per their investigator's judgment.

End of Macitentan (EOM): All subjects treated with macitentan who prematurely discontinue macitentan will have an EOM visit within 1 week after the last dose of macitentan.

Survival Follow-up**:** Applies to subjects who prematurely discontinue regular study visits during Core Period. Survival data will be collected at least yearly after the last regular study visit and until EOCP for Analysis 2 . In these subjects the last survival follow-up contact constitutes their EOS.

End of Core Period (EOCP) Visit**:** This visit will occur in first quarter of 2024 and before the cutoff date for Analysis 2 which will be announced by the sponsor. For subjects who don't enter the Single-Arm Extension Period the EOCP visit constitutes their End-of-Study visit.

**Safety Follow-up Period:** Applies to subjects who prematurely discontinue macitentan or SoC treatment during Core Period or during the single-arm extension period (SAEP). In addition, it applies to subjects at EOS who do not enter the SAEP or who do not go into a PTA or LTE study. It begins immediately after premature end of treatment or after EOCP/EOS and ends at least 30 days later with a safety follow-up telephone call.

Subjects prematurely discontinuing treatment during the Core Period are encouraged to continue participation in the study according to the regular study visit schedule or at least agree to Survival Follow-up until EOCP. Only for subjects whose parent(s) / legal representative withdraw consent to further study participation the safety follow-up telephone call is EOS.

In addition, and as per local practice, unscheduled visits may also take place, in which case study-related information as specified in Section 8.11 will be collected and recorded in the electronic Case Report Form (eCRF).

**Single-arm Extension Period (SAEP):** This period starts at EOCP visit and ends at EOS visit. Subjects who are in the 12-weekly regular visits at EOCP visit, and for whom the investigator judges that macitentan treatment could be beneficial and who fulfill the safety criteria to initiate or continue macitentan treatment are eligible to enter the open-label single-arm extension period.

End of Study (EOS) Visit**:** At the end of the SAEP each subject will come for an EOS Visit within 12 weeks of the Sponsor announcing the end of the study. For subjects who discontinue the study prematurely the last visit or last survival FU contact constitutes their EOS visit.

For subjects who cannot access macitentan, a continued access program will be put in place (e.g., post-trial access [PTA], long-term extension study [LTE]) to allow treatment continuation, if assessed beneficial by the investigator and within local regulations.

For subjects rolling over to PTA or LTE study after the SAEP, the enrollment must occur on the day of the last visit of this study ie, EOS Visit to avoid macitentan treatment

interruption. These subjects will not have a Safety FU call in TOMORROW since their safety follow-up continues in the respective PTA or LTE study.

**Pharmacokinetic (PK) Substudy for Subjects ≥ 2 y.o.**

Participation in the PK substudy is optional for up to 40 subjects ≥ 2 y.o. receiving macitentan.

At steady-state conditions, a PK profile will be collected over 24 hours from subjects ≥ 2 y.o. treated with macitentan. Collected PK data (both PK profiles and trough concentrations) will be regularly assessed using non-linear mixed effects pharmacokinetic modeling during the course of the study to confirm the appropriateness of the selected dosing regimen in subjects older than 2 years. A formal sample size calculation will determine the amount of PK data (full PK profile plus trough samples collected) required to ensure at least 80% power to conclude that exposure in pediatric subjects is as targeted from the knowledge available from adults.

Modeling and simulation have been performed based on the PK data from pediatric subjects older than 2 years and adults to select the appropriate daily dose in subjects below 2 years of age. The modeling and PK data will be reported separately (i.e., not included in the Clinical Study Report [CSR]).

The participation in the PK substudy will be controlled via Interactive Response Technology (IRT) system.

A separate informed consent will be obtained for participation to the PK substudy. Subjects who prematurely discontinue macitentan treatment before the scheduled Visit 3 are excluded from the PK substudy.

**PK Assessment for Subjects < 2 y.o.**

All subjects < 2 y.o. will have PK assessments (refer to Section 7.7) to allow adequate characterization of macitentan PK and dose regimen in this age cohort.

Sparse and patient-centric sampling will be utilized to reduce the burden of extensive blood collections in young children. Samples over 24 hours after the first dose and two trough samples at steady-state will be collected. Collected PK data will be regularly assessed using non-linear mixed effects pharmacokinetic modeling during the course of the study to confirm the appropriateness of the selected dosing regimen in these subjects.

Macitentan and ACT-132577 (aprocitentan) concentrations will be summarized descriptively and reported in the CSR. The population PK analysis will be reported separately.

### Study Duration

The study starts with the first act of recruitment (i.e., Informed Consent Form [ICF] signed) and ends with the last visit/contact of the last subject. The study is considered completed when the last subject completes the study (i.e., last EOS visit).

This is a calendar-driven study and time points of analysis depend on dates to meet regulatory commitment.

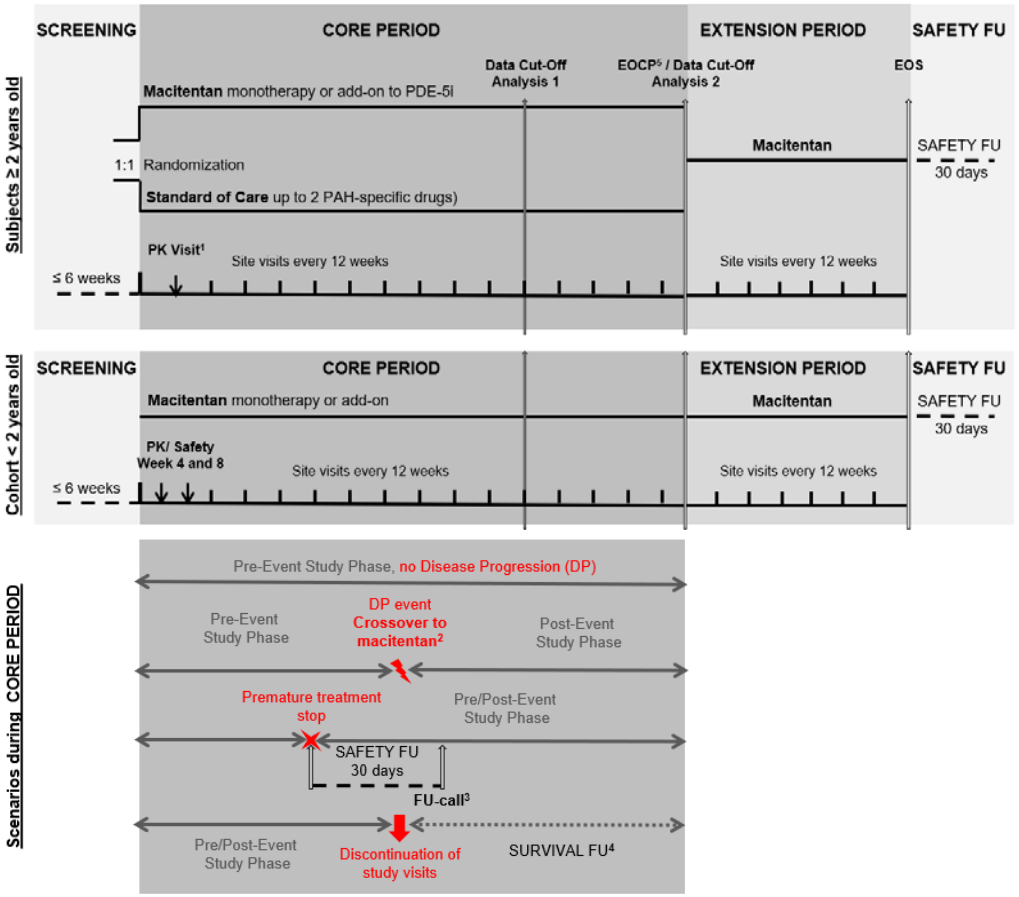
Study duration for each individual subject will be based on their time of enrollment. All subjects are planned to remain in the study until the cutoff date for Analysis 2 in 2024. Thereafter, if it is considered in the best interest of the subject, continuation in the open-label single-arm extension period with macitentan will be offered.

Subject participation in the Core Period at timepoint of Analysis 2 will be up to 7 years. Participation in the SAEP will be at least 24 weeks.

Overall study duration (including Core Period and extension period) will be a minimum of 7 years (from first subject screened until last subject last EOS visit).

The overall study design is depicted in Figure 1.

## Figure 1: Study Design




EOS end of study; FU follow up; IV intravenous; PAH pulmonary arterial hypertension; PDE 5i phosphodiesterase Type 5 inhibitor; PK pharmacokinetics; SC subcutaneous.

1 The PK Visit will occur under steady state conditions (i.e., ≥ 10 days of same macitentan dose), as described in Section 8.4.

2 After disease progression confirmed by the CEC, the subject enters the Post Event Study Phase. In the macitentan group, the study treatment will continue during this Post Event Study Phase until EOS. Subjects in the SoC group will be offered **cross-over to macitentan**, if this is considered in the best interests of the subject per their investigator's judgement. The Cross over Visit is described in Section 8.10.

3 Subjects discontinuing macitentan or SoC treatment prematurely have a Safety FU call 30 days (+ 1 week) after the treatment stop. End of standard of care will be declared, if a planned PAH specific drug class is discontinued, or if any additional PAH specific drug class is added, or if subjects cross over to macitentan after CEC confirmed disease progression.

4 Subjects discontinuing site visits during the Core Period will have Survival FU contacts at least yearly to collect vital status.

5 Subjects still in the 12 weekly visit schedule at Analysis 2 will come for the EOCP Visit before the cutoff date announced by the Sponsor, and will be offered to enter the single arm extension period. The eligibility to continue/start macitentan in the single arm extension period (SAEP) must be confirmed as described in Section 8.13.

For subjects who continue macitentan or SoC treatment until EOCP but do not enter the SAEP, the EOCP will constitute their EOS Visit and they will have a Safety FU call 30 days (+ 1 week) after EOS.

Note: For subjects who after EOS in the SAEP cannot access macitentan continued access program will be put in place (e.g., post trial access [PTA] or long term extension [LTE] study) to allow treatment continuation as per local regulations. For subjects who complete the study treatment and who are eligible for a continued access program (PTA or LTE study), enrollment into the continued access program should occur on the same day as the EOS Visit to avoid macitentan treatment interruption and the Safety FU period will be waived.

## 3.2 Study Design Rationale

As per ICH [ICH E11 Guidelines] the efficacy of medications approved in adults can be assumed to be comparable for the same indication in children if the disease process is similar in the two populations, which is the case for PAH [Barst 2011]. A long-term, open-label controlled trial investigating the PK, safety and evaluating the totality of efficacy of macitentan in children is deemed appropriate.

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 and mortality as the most clinically meaningful outcomes in PAH [Ivy 2013, Chakinala 2013]. Successful use of such endpoints in adult studies [Pulido 2013, Sitbon 2015] suggests that it is worthwhile to also consider similar endpoints and assessments in the pediatric population. However, based on disease rarity hampering recruitment, and current management of pediatric PAH patients leading to slow disease progression powering a pediatric study to show delay in disease progression can take more than 10 years and is not considered feasible.

It is deemed necessary to establish the PK of macitentan in children to allow correct dosing and to evaluate efficacy of macitentan considering the totality of evidence including all efficacy endpoints.

The open-label design with SoC as a comparator arm has considerable ethical and scientific merit: (i) it does not impose specific therapies as comparator in the absence of well documented effectiveness of any PAH-specific therapy in children and approval of these globally, (ii) it allows all children to be treated with either best SoC according to investigator's judgment or with macitentan, a compound that has demonstrated efficacy on delaying disease progression in adults, and (iii) it allows inclusion of a wide population representative of the overall pediatric PAH patients regardless of their previous PAH-specific therapy.

In order to minimize potential bias related to the open-label design, some aspects of the study conduct have been outsourced to Contract Research Organizations (CROs). The firewalls put in place between blinded and unblinded study team members are described in a dedicated Firewall Charter. The Sponsor representatives preparing and reviewing the Statistical Analysis Plan (SAP) for the Core Period will remain blinded until the Analysis 1 results are available. Sponsor representatives accountable for Safety Monitoring will review the SAP sections related to safety analysis and will have partial access to unblinding information as described in the Firewall Charter.

Medical treatment guidelines for pediatric PAH recommend the use of PAH-specific combination therapy for children who have progression of PAH symptoms or clinical

evidence of right heart failure [Rosenzweig 2019]. However, not all study subjects have access to an ERA treatment. Therefore, after CEC-confirmed disease progression macitentan is offered to those subjects who may benefit from such treatment per their investigator's judgment. It is expected that this will improve subject retention. In order to reduce potential reporting bias for disease progression in the SoC group, macitentan will only be offered after the event has been confirmed by the blinded CEC.

Enrollment of children < 2 y.o. can only be initiated with Protocol V9 since sufficient PK data was needed in older children in the TOMORROW study to determine the daily macitentan doses necessary to reach similar exposure in the youngest age cohort as described in Section 1.2.2. Consequently, the recruitment period for children < 2 y.o. is marginally shorter as compared to the recruitment period of the older age groups. In addition, the age cohort < 2 y.o. is rare and PAH diagnosis is lengthy since transient PH must be excluded and PAH after shunt repair cannot be reliably diagnosed within the first few months after surgery delaying the diagnosis [Haarman 2020, Ivy 2013, Kwiatkowska 2020]. Aiming to establish the PK and safety of macitentan also in patients < 2 y.o. those will be directly enrolled into the macitentan arm without randomization. This will ensure that data are generated on macitentan and not on standard of care. Efficacy assessments will still be performed as applicable in this age cohort.

The single-arm open-label extension period allows seamless continuation of treatment and access to the study drug for all subjects if this is considered in their best interest and trial results do not reveal any harmful effect in the pediatric population.

## 3.3 Site Personnel and Their Roles

The following tasks must be carried out by a physician as delegated by the principal investigator (PI):

- Informed consent process (study physician must be involved in the process)
- Specific protocol procedures including:
  - decision on subject eligibility,
  - macitentan prescription (decision on start and discontinuation),
  - reporting of SAEs,
  - reporting of disease progression,
- eCRF sign off.

**Note:** in some regions an Advanced Practice Role (or an equivalent), such as a registered nurse practitioner, can perform the consent interview and sign the ICF without a second signature of a physician. However, there must be documented acceptance by the respective Independent Ethics Committee (IEC) / Institutional Review Board (IRB), and Delegation of Authority must be given by the PI. A physician must be available to answer any medical

questions or questions regarding alternative therapies and this must be documented in the source data of the subject.

## 3.4 Study Committees

An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety, tolerability and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with the highest scientific and ethical standards. The IDMC will be fully operational prior to enrolment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC Charter.

The IDMC may recommend modifications of the protocol (to enhance subject safety) or recommend early termination of the study if major concerns arise about subject safety at any time during the course of the study or during any other study with the same investigational drug.

An Independent Statistical Analysis Center (ISAC, not otherwise involved with study conduct or statistical analysis) will have access to the randomization list and will generate the monitoring reports exclusively for review by the IDMC.

The ISAC will also be in charge of monitoring, in collaboration with the IDMC, the number of disease progression events occurring over time, in order to make appropriate predictions for number of events anticipated by timepoint of Analysis 1 and Analysis 2.

A CEC consisting of independent PAH experts also including pediatricians has been appointed to review and adjudicate in a blinded fashion the secondary endpoints related to disease progression [see Section 6.1.2]. The composition and operation of the CEC is described in the CEC Charter. The CEC Coordinator will provide feedback on the adjudication decisions of the events to the investigators. In order to ensure exhaustive and systematic adjudication, in addition to disease progression events reported by the investigator [refer to Section 8.9], subject cases will be submitted to the CEC if at least one of the following conditions is reported by the investigator: death, (S)AEs denoting PAH worsening/ right heart failure (pre-specified list of MedDRA terms in CEC Charter), interventions such as lung transplantation, atrial septostomy and Pott's anastomosis, new administration of at least one PAH-specific medication, initiation of IV diuretics or chronic use of oxygen. Generic/brand names of PAH-specific medications will be blinded to the CEC to reduce assessment bias. If there is any change to key data (defined in the CEC Charter) or new key data become available after a first submission of a subject case to the CEC, the CEC Coordinator re-submits the case for re-adjudication.

An independent Baseline Characteristics Adjudication Committee (BCAC) will review and approve the randomization before macitentan start for children < 2 y.o. / eligibility of

subjects with PAH with co-incidental CHD i.e., small atrial septal defect, ventricular septal defect or patent ductus arteriosus which themselves do not account for the development of elevated PVR. This independent review is governed by a Charter.

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

# 4 SUBJECT POPULATION

## 4.1 Subject Population Description

Study AC-055-312 includes male and female pediatric subjects aged ≥ 1 month to <18 years.

Subjects with iPAH or hPAH, as well as PAH associated with CHD, drug or toxin-induced PAH, or CTD and PAH associated with HIV are enrolled if they are of WHO FC I, II, or III.

Eligible subjects are PAH-specific treatment-naïve, or already treated with PAH-specific monotherapy or double combination therapy excluding macitentan and IV/SC prostanoids. Cohort of children < 2 y.o. is allowed to enter on macitentan.

Subject randomization will be stratified according to clinical variables outlined in Section 3.1.

## 4.2 Rationale for the Selection of the Study Population

Pediatric subjects with PAH across all age groups and of all etiologies relevant in children [refer to Section 4.1] are enrolled to cover a generalizable pediatric PAH population. Within the subgroup of PAH associated with CHD, the protocol excludes patients with Eisenmenger syndrome as well as patients with open left-to-right shunts due to lack of sufficient adult data supporting efficacy of macitentan in children. Subjects with Down Syndrome, representing an important subset of subjects with CHD, will also be included. This provides an opportunity to assess the efficacy and safety of a targeted PAH therapy in this subgroup rarely evaluated in randomized clinical trials.

Macitentan has shown benefit in both treatment-naïve adults as well as in adults previously treated with PAH-specific therapies. A similar benefit is anticipated in children. Subjects on triple combination therapy are excluded because treatment escalation is part of the clinical worsening component of the secondary efficacy endpoint and the possibility for further escalation in such subjects would otherwise be very limited.

WHO FC I, II, or III subjects are targeted since they classify for monotherapy or double combination therapy with a PAH-specific drug. Inclusion of WHO FC I and II subjects will allow for the investigation of occurrence of disease progression in less advanced disease. In children, PAH is associated with rapid disease course justifying early targeted therapy [Lammers 2007].

## 4.3 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject:

1. Signed informed consent by the parent(s) or legally designated representative AND assent from developmentally capable children prior to initiation of any study-mandated procedure.
2. Criterion modified per Amendment 8 Version 9:
   Males or females between ≥ 1 month and < 18 years of age.
3. Criterion modified per Amendment 8 Version 9:
   Subjects with body weight ≥3.5 kg at randomization.
4. Criterion modified per Amendment 6: PAH diagnosis confirmed by historical RHC (mPAP ≥ 25 mm Hg, and PAWP ≤ 15 mm Hg, and PVRi > 3 WU x $m^2$), where in the absence of pulmonary vein obstruction and/or significant lung disease PAWP can be replaced by LAP or LVEDP (in absence of mitral stenosis) assessed by heart catheterization.
5. PAH belonging to the Nice 2013 Updated Classification Group 1 (including subjects with Down Syndrome) and of following etiologies:
   - iPAH
   - hPAH
   - PAH associated with CHD:
     PAH with co-incidental CHD (confirmed by BCAC)
     Post-operative PAH (persisting/recurring/developing ≥ 6 months after repair of CHD)
   - Drug or toxin-induced PAH
   - PAH associated with HIV
   - PAH-aCTD
6. WHO FC I to III.
7. PAH-specific treatment-naïve subjects or subjects on PAH-specific treatment (mono-therapy or combination of two therapies)*.
8. Females of childbearing potential must have a negative pregnancy test at Screening and at Baseline, and must agree to undertake monthly pregnancy tests, and to use a reliable method of contraception (if sexually active) up to EOS .

***Note to inclusion criterion 7:** Treatments other than PDE-5 inhibitors, such as prostanoids, cannot be continued in the macitentan arm, and therefore will have to be stopped [see Section 5.1.1] if the patient is randomized into the macitentan arm. The appropriateness of stopping such treatment must be assessed by the investigator before screening the patient for the study and should not be done for the sole objective of selecting a patient for the study.

## 4.4 Exclusion Criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject:

**Etiology**

1. Subjects with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn.
2. Subjects with PAH associated with open shunts, as specified below:
   a. Eisenmenger syndrome
   b. Moderate to large left-to-right shunts.
3. Subjects 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 subjects with Fontan-palliation.
4. Subjects with pulmonary hypertension due to lung disease (e.g., bronchopulmonary dysplasia).
5. Criterion added per Amendment 8 Version 9:
   Subjects with known diagnosis of bronchopulmonary dysplasia.

**Treatment and intervention**

6. Subjects receiving a combination of > 2 PAH-specific treatments at randomization.
7. Treatment with IV or SC prostanoids within 4 weeks before randomization, unless given for vasoreactivity testing.
8. Criterion added per Amendment 8 Version 9:
   In children ≥ 2 y.o.: Previous treatment with macitentan at any time.
9. Treatment with another investigational drug within 4 weeks prior to randomization.
10. Any PAH-related surgical intervention planned, or subjects listed for organ transplantation related to PAH.
11. Treatment with strong inducers of CYP3A4 such as rifabutin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort (hypericum perforatum), within 4 weeks prior to randomization.
12. Systemic treatment with strong inhibitors of CYP3A4 such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone,

nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole within 4 weeks prior to randomization.

13. Criterion modified per Amendment 3.1 Version 4.1:
    Systemic treatment with moderate dual CYP3A4/ CYP2C9 inhibitor (e.g., fluconazole and amiodarone), or administration of a combination of a moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (e.g., miconazole, piperine) within 4 weeks prior to randomization.

**Baseline abnormalities**

14. Subjects with pulmonary vein stenosis.
15. Known concomitant life-threatening disease with a life expectancy < 12 months.
16. Hemoglobin or hematocrit < 75% of the lower limit of normal range (LLN).
17. Serum AST and/or ALT > 3 × ULN.
18. Criterion modified per Amendment 6 Version 7: Severe hepatic impairment, e.g., Child-Pugh Class C [see Appendix 1].
19. Clinical signs of hypotension which in the investigator's judgment would preclude initiation of a PAH-specific therapy.
20. Criterion added per Amendment 6 Version 7: Severe renal insufficiency (estimated creatinine clearance <30 mL/min or serum creatinine >221 μmol/L)

**Pregnancy and breastfeeding**

21. Pregnancy (including family planning) or breastfeeding.

**Other categories**

22. Known hypersensitivity to ERAs, or any of the excipients.
23. Drug or substance abuse, or any condition that, in the opinion of the investigator, may prevent compliance with the protocol or adherence to study treatment.

Note: The assessment for hepatic impairment at Screening (Child Pugh Score) must be fully documented for patients with hepatic impairment as part of their medical history and/or clinical signs and evidence (from the local lab) of hepatic impairment.

## 4.5 Criteria for Female Subjects of Childbearing Potential

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 subjects of childbearing potential who are sexually active must use a reliable method of contraception.

### 4.5.1 Definition of Childbearing Potential

A female subject is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Prepubescence*
- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Tubal sterilization[#]
- Premature ovarian failure confirmed by a specialist.
- XY genotype or any other genetic disorder associated with permanent sterility, uterine agenesis.

* Childbearing potential status will be assessed at each visit and recorded in the eCRF. For females who are not considered to be of childbearing potential due to pre-pubescence, the pubertal status must be reassessed at each visit.

[#] Tubal sterilization may not fully protect against pregnancy [Bouillon 2018]. Therefore, subjects who had a tubal sterilization will have monthly pregnancy tests but are exempted from use of contraceptives.

The reason for not being of childbearing potential will be recorded in the eCRF.

### 4.5.2 Acceptable Methods of Contraception

In both treatment arms for female subjects of childbearing potential [definition in Section 4.5.1] and who are sexually active the use of contraception is mandatory during Screening and up to EOS.

In the macitentan group, one of the following options for contraception must be used:

| Option 1* | Option 2* | Option 3 |
|---|---|---|
| **One method from this list:** | **One method from this list:** | **One method from this list:** |
| Standard intrauterine device (IUD) (Copper T380A IUD) | Estrogen and progesterone oral contraceptives ("the Pill") | Diaphragm with spermicide |
| Intrauterine system (LNg 20IUS: progesterone IUS) | Estrogen and progesterone transdermal patch | Cervical cap with spermicide |
| Progesterone implant | Vaginal ring | **PLUS one method from this list:** |
| | Progesterone injection | Male condom |
| | **PLUS one method from this list:** | |
| | Male condom | |
| | Diaphragm with spermicide | |
| | Cervical cap with spermicide | |

* Option 1 and Option 2 are classified as highly effective methods (< 1% failure rate).

In the SoC group, reliable methods of contraception are defined as per local medical practice. Subjects in the SoC group who initiate macitentan study treatment (i.e., at Cross-over or at EOCP) must use either Option 1, 2 or 3.

If hormonal contraception is one of the methods used, then it must have been initiated at least 4 weeks prior to Randomization (Visit 2).

In subjects who become sexually active any time after randomization and who are of childbearing potential, contraceptive method(s) that are immediately effective must be used initially (e.g., Option 3 in macitentan group). This method(s) can be replaced but must continue until the new method of contraception becomes effective.

The methods of contraception used (including non-pharmacological methods) must be recorded in the eCRF.

## 4.6 Medical History

The study indication, i.e., PAH, and related signs and symptoms, are not recorded as medical history but on dedicated eCRF pages. Relevant medical history other than PAH, as defined below, must be recorded in the eCRF:

- Any condition that is currently treated (i.e., on therapy at enrollment)
- Any serious medical conditions in the past 6 months
- Chronic medical conditions (e.g., diabetes, seizure, asthma)
- Any life-threatening condition in the past (e.g., sepsis)
- Any condition in the past that resolved with sequelae

# 5 TREATMENTS

## 5.1 Study Treatment

### 5.1.1 Investigational Treatment: Macitentan - Description and Rationale

Macitentan, open-label, is administered once daily via oral route in dispersed form. Daily doses are given according to the body weight category for subjects of ≥ 2 y.o. and according to age in the subjects of < 2 y.o. [refer to Section 5.1.5].

Clinical Formulation: Macitentan is provided as a dispersible tablet of following dose strengths: 0.5 mg, 2.5 mg, and 5 mg. This formulation is only used in subjects of at least 6 months of age and will be controlled via IRT.

Final Market Image (FMI): Macitentan dispersible tablet will be available in new dose strengths of 1 mg and 2.5 mg with different shape and debossing. The FMI will replace the clinical formulation once sufficient stability data is available and local approval, if applicable, has been obtained. This formulation will be used in all subjects (≥ 1 month of age).

The pediatric macitentan doses for children above 2 years were determined using population pharmacokinetic modeling that considered allometric scaling and maturation of clearance [D-14.468]. The resulting doses, to be given according to body weight category, were selected to achieve systemic exposure observed in adults with PAH treated with macitentan 10 mg once daily in a majority of the pediatric population. The study has been started with children above 2 years of age as they have more mature hepatic and renal function and, therefore, the metabolism and clearance of drugs can be better predicted.

In a substudy of up to 40 subjects distributed over the different age ranges between 2 and < 18 years (across age categories: 2 to < 7 years, 7 to < 12 years, and 12 to < 18 years), PK profiles will be assessed over a period of 24 hours at steady-state conditions.

Dosing regimen for children below 2 y.o. was proposed using population and PBPK approach that considered maturation of CYP enzyme functions in infants and young children between 1 month and 2 y.o. Exposure to macitentan was simulated following administration of different potential doses, and doses, to be given according to age, were selected to provide similar exposure to that of adult subjects receiving 10 mg once daily.

PK assessment will be performed in all children under 2 y.o. For this cohort of subjects, sparse and patient-centric sampling will be used to lower the burden of extensive blood collection in young children. Blood concentrations after a single dose of macitentan over the first 24 hours and two trough concentrations at steady-state will be collected. Macitentan and ACT-132577 (aprocitentan) concentrations will be summarized descriptively per timepoint and a population PK analysis will be done separately.

Scales used to assess the body weight of subjects must be calibrated and respective calibration certificates must be available prior to the first subject being randomized at the site. Scales must be calibrated annually.

Subjects randomized to macitentan are treated as follows:

- Subjects with no PAH-specific therapy at randomization will receive macitentan monotherapy.
- Subjects on PDE-5 inhibitor monotherapy at randomization will receive macitentan as add-on therapy.
- Subjects on ERA or oral/inhaled prostanoid monotherapy at randomization will receive macitentan monotherapy instead.
- Subjects on PDE-5 inhibitor in combination with another PAH-specific therapy at randomization will receive the combination of macitentan and the PDE-5 inhibitor.

In subjects ≥ 2 y.o., a PDE-5 inhibitor is the only allowed PAH-specific background medication until disease progression in the macitentan arm. All other PAH-specific medications must be stopped. If the subject is on an ERA treatment, refer to instructions in Appendix 2 for transition to macitentan. If the patient is on a prostanoid treatment during Screening, this treatment must be discontinued if they are randomized to macitentan. In order to avoid any rebound effect of pulmonary hypertension, prostanoids should be cautiously downtitrated after randomization until complete discontinuation, as per local practice. After randomization, new PAH-specific medications, and/or continuous oxygen and/or IV diuretics are recommended to be initiated only if the condition of the secondary efficacy endpoint (PAH disease progression) is met per investigator's judgment. However, non-adherence to these recommendations does not constitute per se a reason for premature study discontinuation. All efforts should be made to keep the patients in the study according to the original schedule of assessments.

After EOCP (i.e., during the SAEP) those medications can be initiated at any time.

In subjects < 2 y.o., oral/ inhaled prostanoid treatment are also allowed as PAH-specific background therapy in all study periods.

### 5.1.2 Comparator: Standard of Care - Description and Rationale

The study protocol does not impose any predefined comparator drug. Subjects randomized to the control arm are treated with SoC as per site's clinical practice which may comprise treatment with PAH non-specific treatment and/or up to two PAH-specific medications excluding macitentan and IV/SC prostanoids.

Subjects randomized to the SoC arm will be treated as follows:

- Subjects only on PAH non-specific medications at randomization will continue on their medications.
- Subjects on PDE-5 inhibitor and/or on other PAH-specific treatment (such as ERA, or inhaled/oral prostanoids) at randomization will continue on their medications.
- For all subjects, additional PAH-specific therapy (excluding macitentan and IV/SC prostanoids), if prescribed during the screening period, can be initiated.

The investigator documents the SoC in the IRT system before randomization.

Dose adjustment to reach the targeted dose or sequential introduction of combination therapy is allowed as prescribed by the investigator in IRT prior to randomization. Once the target maintenance dose is achieved, the regimen should be stable except in the presence of AEs or change to the subject's body weight. In these cases dose adjustments, interruptions and permanent discontinuation follow local practice.

After randomization, new PAH-specific medications (not prescribed as part of the SoC regimen), and/or continuous oxygen and/or IV diuretics are recommended to be initiated only if the condition of the secondary efficacy endpoint (PAH disease progression) is met as per judgment of the investigator. Changes within the same drug class are allowed. However, non-adherence to these recommendations does not constitute per se a reason for premature study discontinuation. All efforts should be made to keep the patients in the study according to the original schedule of assessments. End of SoC will be declared if a planned PAH-specific drug class is discontinued or if any additional PAH-specific drug class is added.

In the presence of a CEC-confirmed disease progression event, the subjects in the SoC arm will be offered to start macitentan treatment, if this is in their best interest per their investigator's judgment [refer to Section 8.10]. Cross-over to macitentan study treatment will be offered at the EOCP visit as per best interest of the subject. If the subject is on an

ERA treatment at the time of cross-over to macitentan, refer to instructions in Appendix 2 for transition to macitentan.

PAH-specific medications are reported in the eCRF as described in Section 5.2.2.

Current PAH-specific treatments for children with PAH are described in Section 1.2.3. The rationale for the use of SoC as comparator is provided in Section 3.2.

### 5.1.3 Treatment Assignment

After having obtained informed consent and assent (if applicable) at Visit 1, the investigator/delegate contacts the IRT system and obtains a subject number from the IRT system which will identify the subject throughout the study. After having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT at Visit 2 to document the SoC and to subsequently randomize the subject ≥ 2 y.o. The IRT assigns a randomization number to the subject. If the subject is randomized to the macitentan group the IRT also assigns the treatment pack(s) number(s) assigned by the randomization list to the randomization number. If applicable, damaged blister packs are recorded by the investigator/delegate in the IRT system and are not allocated to any study subject. If the subject is randomized to the SoC group, standard of care treatment is continued or initiated as documented by the investigator. For subjects in the SoC group who receive macitentan after disease progression is confirmed by the CEC or during the SAEP, the IRT assigns the treatment pack(s) number(s) according to the subject's body weight group.

Subjects ≥ 2 y.o. are assigned in a 1:1 ratio to the macitentan or the SoC group. Randomization is stratified according to ongoing/planned ERA treatment at randomization (yes vs no) and WHO FC at randomization (I/II vs III).

The enrollment of subjects with SoC in a control group containing ERAs is limited to maximum of 40% using IRT system.

The randomization list is generated by the Central Randomization CRO.

The cohort of children < 2 y.o. at Visit 2 will enter the macitentan arm without randomization. No ERA cap will be set for this cohort. The investigator/ delegate contacts the IRT at Visit 2 after eligibility has been confirmed, and IRT assigns the treatment pack number according to the subject's age. At 12-weekly visits when the subject is at least 2 years old the IRT will assign the macitentan pack number as per subject's body weight group.

### 5.1.4 Blinding

Not applicable. Measures taken to reduce the bias inherent to open-label design are described in Section 3.2.

### 5.1.5 Macitentan Administration

Macitentan is administered after dispersion of tablet(s) in water even to subjects who can swallow tablets. The dose is adjusted to the subject's age (for those < 2 y.o.) or to the subject's body weight (for those ≥ 2 y.o.) at treatment assignment as described in Table 6 and Table 7.

At each 12-weekly study visit (i.e., excluding Visit 3) the subject's age or body weight (as applicable) must be verified for potential dose adjustment. Change in age or weight category is entered into the IRT system which will provide new macitentan study treatment pack(s).

The dispersion must be reconstituted by the caregiver (e.g., parent) prior to administration. Subjects who are developmentally capable may prepare the drug dispersion themselves.

Whole tablet(s) are dispersed in water and administered orally (e.g., via spoon). The full daily dose is taken at a single occasion (refer to the Pharmacy Manual for TOMORROW study).

The first dose in the macitentan group is administered at Visit 2 (i.e., within 24 hours after macitentan treatment pack has been assigned to the subject) and under the guidance of the investigator or delegate. Thereafter, macitentan is administered once daily and irrespective of time of food intake but at approximately the same time of the day.

Parent(s) / legally designated representative and subjects are instructed that macitentan should not be administered on days of study Visits 3 (at steady-state) and 4 (Week 12) until the pre-dose PK sample has been collected and as instructed by the study-site person.

For cohort of children < 2 y.o., the parent(s) / legally designated representative is instructed not to administer macitentan at Week 4 and Week 8 visits until the pre-dose PK sample has been collected.

Instructions regarding dose adjustment and the need for interruption or discontinuation of macitentan are provided in Sections 5.1.8, 5.1.9, and 5.1.10.

**Table 6: Dosing Scheme for Clinical Formulation**

| Age [month] | Body Weight [kg] | Daily dose | Number of tablets to be dispersed |
|---|---|---|---|
| ≥ 1 and < 6 | not applicable (NA) | NA | NA |
| ≥ 6 and < 24 | not applicable | 2.5 mg | 1 x 2.5 mg |
| ≥ 24 | ≥ 10 kg and < 15 kg | 3.5 mg | 2×0.5 mg & 1×2.5 mg |
| | ≥ 15 kg and < 25 kg | 5.0 mg | 1 x 5.0 mg |
| | ≥ 25 kg and < 50 kg | 7.5 mg | 1×2.5 mg & 1x5.0mg |
| | ≥ 50 kg | 10.0 mg | 2×5.0 mg |

**Table 7: Dosing Scheme for Final Market Image**

| Age [month] | Body Weight [kg] | Daily dose | Number of tablets to be dispersed |
|---|---|---|---|
| ≥ 1 and < 6 | not applicable | 1.0 mg | 1 x 1.0 mg |
| ≥ 6 and < 24 | not applicable | 2.5 mg | 1 x 2.5 mg |
| ≥ 24 | ≥ 10 kg and < 15 kg | 3.5 mg | 1 × 1.0 mg and 1×2.5 mg |
| | ≥ 15 kg and < 25 kg | 5.0 mg | 2 x 2.5 mg |
| | ≥ 25 kg and < 50 kg | 7.5 mg | 3×2.5 mg |
| | ≥ 50 kg | 10.0 mg | 4 × 2.5 mg |

### 5.1.6 Macitentan Supply

Manufacture, labeling, packaging, and supply of macitentan will be conducted according to Good Manufacturing Practice, Good Clinical Practice (GCP), and any local or national regulatory requirements.

All macitentan supplies are to be used only in accordance with this protocol, and not for any other purpose.

The following sections are only applicable for subjects who receive macitentan study treatment.

#### 5.1.6.1 *Macitentan Packaging and Labeling*

*5.1.6.1.1 Macitentan packaging*

Macitentan is provided as dispersible tablets and supplied in childproof blister packs.

*5.1.6.1.2 Macitentan labeling*

Macitentan is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

#### 5.1.6.2 *Macitentan Distribution and Storage*

Macitentan supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label.

#### 5.1.6.3 *Macitentan Dispensing*

The subjects will receive enough macitentan to cover the period up to the next scheduled 12-weekly visit (i.e., excluding Visit 3 for PK). Subject's parent(s) / legal representative are asked to return all used, partially used, and unused study treatment blister packs at each scheduled visit (except Visit 3). The protocol-mandated study treatment dispensing/return procedures may not be altered without prior written approval from the Sponsor. An accurate record of the date and amount of macitentan dispensed to each subject must be available for inspection at any time.

#### 5.1.6.4 *Macitentan Return and Destruction*

On an ongoing basis and on termination of the study, the monitor, i.e., Clinical Research Associate (CRA) will collect used and unused treatment packs, which will be sent to the warehouse for reconciliation. In certain circumstances, used and unused macitentan containers may be destroyed at the site once study treatment accountability is finalized and has been checked, and written permission for destruction has been obtained.

### 5.1.7 Macitentan Accountability and Compliance With Macitentan Study Treatment

Sections 5.1.7.1 and 5.1.7.2 are only applicable for subjects who receive macitentan study treatment.

#### 5.1.7.1 *Macitentan Drug Accountability*

The inventory of macitentan dispensed to and returned by the subject (i.e., study treatment accountability) must be performed by the site personnel on the day of the visit and before dispensing further macitentan in order to ensure that the subject is compliant with study requirements. The site personnel records this inventory on the study treatment dispensing and accountability log and in the eCRF. The CRA checks these entries during monitoring visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each macitentan unit (blister) dispensed to the subject:

- Unique blister-card identifying number of the dispensed blisters
- Date dispensed / number of tablets dispensed
- Date returned / number of tablets returned

All macitentan supplies, including partially used or empty blister packs must be retained at the site for review by the CRA.

If the parent/ legally designated representative of the subject forgets to bring the remaining macitentan to a study visit, he/she must be instructed that the subject should not receive any tablet from the remaining study treatment blister pack(s) and to return it/them at the next visit.

#### 5.1.7.2 *Macitentan 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 subject (if developmentally capable) and re-educate them on correct administration of study treatment. Details of such discussion must be documented in the subject's file.

If the compliance with study treatment 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 subject (if developmentally capable), the reasons for this non-compliance and discuss actions to be taken to avoid re-occurrence. This discussion and its outcome must be documented in the source documents.

### 5.1.8 Macitentan Dose Adjustments and Interruptions

Macitentan dose adjustments other than for change in age category for subjects < 2 y.o. and for weight category for subjects at least 2 y.o. are not permitted.

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 5.1.10.

If macitentan is interrupted by the subject 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.

Dose adjustments of other PAH-specific medications needed due to the subjects' change in body weight or due to an AE are performed as per local practice.

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

### 5.1.9 Macitentan: Premature Discontinuation of Study Treatment

The decision to prematurely discontinue macitentan before EOS may be made by the parent(s) / legally designated representative of the subject, the subject (who is developmentally capable to assent or who comes of age), the investigator, or the Sponsor personnel. The main reason and whether discontinuation of macitentan is the decision of the subject (i.e., parent[s] / legally designated representative, e.g., for tolerability or efficacy reasons), the investigator (e.g., due to pre-specified macitentan discontinuation

criteria, an AE or lack of efficacy), or the Sponsor (e.g., 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 during the Core Period does not constitute per se a reason to withdraw from the study. In case of premature discontinuation of macitentan during the Core Period, every attempt should be made to keep subjects in the study according to the original schedule of assessment until the cutoff date for Analysis 2 (EOCP visit). 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 9.2), vital status will be collected at least yearly (i.e., survival FU) until the cutoff date for Analysis 2 [see Section 8.17], 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 subject's rights.

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

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

Study-specific criteria for discontinuation of macitentan are described in Section 5.1.10.

Withdrawal from the study and medical care of subjects withdrawn from the study are described in Sections 9.2 and 9.4, respectively.

### 5.1.10 Study-specific Criteria for Interruption / Premature Discontinuation of Macitentan Study Treatment

A) Pregnancy

If a female subject becomes pregnant while on macitentan, study treatment must be discontinued immediately, and a Pregnancy Form must be completed [see Section 10.3]. The investigator will discuss with the subject and her parent(s) / legally designated representative the appropriate follow-up medical care.

B) Liver aminotransferases abnormalities

*Interruption of study treatment*

Macitentan study treatment must be interrupted in the following cases:

- Aminotransferases (i.e., ALT and/or AST) ≥ 3 and < 8 x 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 x ULN
- Aminotransferases ≥ 3 x ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever)
- Aminotransferases ≥ 3 x ULN and associated increase in total bilirubin ≥ 2 x 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 (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (e.g., 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]. 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 an SAE. If these abnormalities are serious hepatic events of special interest they will be reviewed by an ILSDRB.

C) Hemoglobin abnormalities

If there is a decrease in hemoglobin from Baseline* of > 20 g/L during treatment with macitentan, a re-test 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.

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

D) Start of an ERA / strong CYP3A4 inducer / strong CYP3A4 inhibitor / investigational product

*Interruption of study treatment*
If any strong inhibitors of CYP3A4 are given, macitentan must be interrupted from first dose of 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 and a moderate CYP2C9 inhibitor are given, macitentan must be interrupted as follows:

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

*Permanent discontinuation of study treatment*
Macitentan must be permanently discontinued if an ERA is administered and/or another investigational product is started during study period.

All re-tests (refer to points B, C and D in this section) are sent for analysis to the Central Laboratory and results are transferred electronically to the clinical database. If, however, re-tests are done in the local laboratory, values available before EOS are recorded by the site in the eCRF.

## 5.2 Previous and Concomitant Therapy

### 5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing of informed consent.

A therapy that is study-concomitant is any treatment that is ongoing or initiated after signing of informed consent, or initiated up to EOS.

A therapy comprises medications as well as therapeutic medical interventions such as radiotherapy.

### 5.2.2 Reporting of Previous/Concomitant Therapy in the ECRF

The use of all study-concomitant therapy (including oxygen, blood transfusions, electrolytes, contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines as well as radiotherapy and diagnostic agents such as contrast media) are recorded in the eCRF.

The generic name, start/end dates of administration (as well as whether it was ongoing at randomization/Visit 2 and/or EOS), route and indication are recorded in the eCRF.

Previous therapy must be recorded in the eCRF if discontinued less than 4 weeks prior to signing the informed consent.

*PAH-related treatments and interventions*

Previous medications and interventions related to PAH treatment (i.e., PAH-specific medications such as ERAs, PAH non-specific treatment such as inotropes, diuretics, anticoagulants, oxygen, etc) are reported in the eCRF if stopped less than 48 weeks prior to signing informed consent.

For PAH-specific treatment, and for oxygen and diuretics it is mandatory to also record the dose in the eCRF.

PAH-specific medications prescribed as planned SoC will be identified in the eCRF. PAH-related non-pharmacological interventions such as atrial septostomy, Potts' anastomosis, and registration on the list for lung transplantation are recorded on dedicated pages for disease progression in the eCRF with date of the intervention/registration.

Survival Follow-up: In addition for subjects who prematurely discontinue study visits, PAH-specific treatments administered up to EOS (i.e., last survival follow-up contact) are recorded in the eCRF.

### 5.2.3 Mandatory Concomitant Therapy

In both treatment arms female subjects of childbearing potential who are sexually active [refer to Section 4.5.1] must use reliable contraceptive methods as specified in Section 4.5.2 until EOS or until last Safety FU phone call (whichever is last). If hormonal contraceptives are used, those must be initiated at least 4 weeks before Visit 2 (Randomization).

For subjects who become sexually active any time after randomization and who are of childbearing potential, contraceptive method(s) that are immediately effective must be applied as specified in Section 4.5.2.

### 5.2.4 Allowed Concomitant Therapy

PAH non-specific therapies (e.g., diuretics, anticoagulants, oxygen, calcium channel blockers) and changes to such medications are allowed during all study periods in both treatment arms. For IV diuretics and continuous oxygen therapy refer also to Section 5.2.6 'PAH treatment escalation'.

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

Screening Period: Any PAH-specific therapy (excluding macitentan and IV/SC prostanoids) can be given or initiated as mono- or combination therapy with a maximum of two treatments.

Cohort of children < 2 y.o.: is allowed to use macitentan during Screening.

Core Period:

Macitentan group

Pre-Event SP: PDE-5 inhibitor treatment ongoing at randomization can continue.

Post-Event SP: Any PAH-specific medication (including IV/SC prostanoids), except ERA, can be administered in addition to macitentan.

Cohort of children < 2 y.o.: is allowed to use oral/ inhaled prostanoids concomitantly with macitentan.

SoC group

Pre-Event SP: Any PAH-specific treatment (other than macitentan and IV/SC prostanoids) as either mono- or double combination therapy prescribed as SoC before randomization can be administered.

Post-Event SP: Any PAH-specific medication (including IV/SC prostanoids) can be administered. Macitentan treatment will be offered after CEC confirms disease progression, if this is in the best interest of the subject per their investigator's judgment [refer to Section 8.10].

Single-arm Extension Period:

Any PAH-specific medication except an ERA can be administered in addition to macitentan.

### 5.2.5 Forbidden concomitant therapy

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

- Use of any investigational drug is forbidden from 4 weeks before randomization/Visit 2 and up to EOS in all subjects.
- IV/SC prostanoids are forbidden from 4 weeks before randomization/Visit 2 and during Pre-Event SP in all subjects, except if given for vasoreactivity testing.
- Use of macitentan is forbidden in subjects ≥ 2 y.o. at any time before study entry. In the SoC group, macitentan is forbidden during the Pre-Event SP.
- In subjects ≥ 2 y.o in the macitentan arm, use of any PAH-specific background therapy other than PDE-5 inhibitor is forbidden during the Pre-Event SP. In order to safely stop prostanoids, these medications should be cautiously downtitrated after randomization, as per local practice.

Concomitant use of an ERA (e.g., bosentan, ambrisentan) with macitentan is forbidden during entire study duration.

Cohort of children < 2 y.o.: use of macitentan is allowed at any time before study entry and oral/inhaled prostanoids are allowed as PAH-specific background therapy.

To avoid drug-drug interactions with macitentan the following treatments are forbidden as specified [Macitentan IB].

- Strong inducers of CYP3A4 such as rifabutin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, and St. John's wort (hypericum perforatum) are forbidden from 4 weeks prior to and until randomization/Visit 2, because the efficacy of macitentan could be reduced. After randomization/Visit 2 these medications should be avoided as follows:
  in the macitentan arm until EOM.
  in the SoC arm from 4 weeks before crossing over to macitentan and until EOM

in the SAEP until EOS.

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 such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole is forbidden from 4 weeks prior to and until randomization/Visit 2. After randomization/Visit 2 systemic administration of these medications is forbidden as follows:
  in the macitentan arm until EOM.
  in the SoC arm from 4 weeks before crossing over to macitentan and until EOM.
  in the SAEP until EOS.

- Systemic administration of moderate dual CYP3A4/CYP2C9 inhibitor such as fluconazole and amiodarone, or combination of a moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) together with a moderate CYP2C9 inhibitor (e.g., miconazole, piperine) is forbidden from 4 weeks prior to and until randomization/Visit 2. After randomization/Visit 2 systemic administration of these medications is forbidden as follows:
  in the macitentan arm until EOM.
  in the SoC arm from 4 weeks before crossing over to macitentan and until EOM.
  in the SAEP until EOS.

**Note:** Subjects who at the time Protocol V4.1 became effective were stable on a moderate dual CYP3A4/CYP2C9 inhibitor (e.g., fluconazole, amiodarone) or co-administration of a combination of a moderate CYP3A4 (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole, piperine) were allowed to remain on macitentan treatment if per the investigator's clinical judgment this was in the best interest of the subject, refer to Food and Drug Administration website [FDA 2020].

To avoid any drug-drug interactions with SoC treatments, the investigator should consult respective medication label(s).

The administration of an ERA and/or of any investigational drug must lead to permanent discontinuation of macitentan as described in Section 5.1.10. 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 as described in Section 5.1.10.

### 5.2.6 PAH Treatment Escalation

In the presence of PAH worsening, any PAH-specific treatment can be initiated per investigator's judgment. It is strongly recommended, however, to initiate PAH-specific medications, and/or continuous oxygen and/or iv diuretics only in the presence of disease progression defined per protocol as per judgment of the investigator.

Subjects in the SoC group will be offered macitentan if the CEC confirms disease progression and if this is considered in the best interests of the subject per their investigator's judgment [refer to Section 8.10]. Subjects in the macitentan group will continue receiving macitentan after a CEC-confirmed disease progression event.

During the SAEP, PAH treatment can be escalated as per local practice.

# 6 STUDY ENDPOINTS

## 6.1 Efficacy Endpoints

### 6.1.1 Primary Endpoint

In subjects ≥ 2 years of age in the macitentan arm:

- Trough (pre-dose) plasma concentrations of macitentan and its active metabolite (ACT-132577) at Week 12 (steady-state)

In subjects less than 2 years of age on macitentan:

- Trough concentrations of macitentan and its active metabolite (ACT-132577) at Week 4 (steady-state)

PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight and age group in subjects ≥ 2 y.o. and < 2 y.o., respectively.

### 6.1.2 Secondary efficacy endpoints

The secondary endpoints are described in Sections 6.1.2.1 and 6.1.2.2.

#### 6.1.2.1 *Time to First CEC-confirmed Disease Progression*

Time to the first of the following CEC-confirmed disease progression events occurring between randomization/Visit 2 and EOCP:

- 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 (i.e., 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 (e.g., pneumonia).
* Worsening from Baseline.
[#] E.g., ERA, PDE-5 inhibitor, prostanoid, IP receptor agonist, soluble guanylate cyclase stimulator.

Investigators will be requested to describe the condition of the subject at Baseline in a Baseline narrative. In the presence of disease progression the investigator must prepare a narrative of the subject's condition and perform an echocardiography and test the level of n-terminal pro-brain natriuretic peptide (NT-proBNP). These data together with any other relevant supportive routine assessment (e.g., RHC, magnetic resonance imaging [MRI], uric acid, etc) and potential hospital discharge summary (if applicable) will be provided to the CEC for adjudication [refer to Sections 3.4 and 8.9].

An independent CEC will adjudicate in a blinded fashion all potential disease progression events reported by investigators (as defined in the CEC Charter; see also Section 3.4), determining the components of the event, the relationship of death or hospitalization with PAH as well as the event onset date. The date of the first CEC-confirmed disease progression event will be used for derivation of the disease progression efficacy variable.

#### 6.1.2.2 *Other Secondary Endpoints*

- Time to first CEC-confirmed hospitalization for PAH occurring between randomization/Visit 2 and EOCP.
- Time to CEC-confirmed death due to PAH occurring between randomization/Visit 2 and EOCP.
- Time to death (all causes) occurring between randomization/Visit 2 and Study Closure.

Following secondary endpoints are analyzed up to end of randomized macitentan or SoC + 7 days. Baseline is the last non-missing value observed before or on the day of randomization/ Visit 2

- WHO FC status (I or II vs III or IV) at Week 24.
- Percent of Baseline plasma NT-proBNP at Week 24.
- Change from Baseline to Week 48 in in mean daily time spent in moderate to vigorous physical activity as measured by accelerometry.
- Change from Baseline to Week 24 in tricuspid annular plane systolic excursion (TAPSE), and left ventricular eccentricity index measured by echocardiography (centrally assessed).
- Change from Baseline to Week 24 in Quality of Life as measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15)[1].

### 6.1.3 Exploratory Endpoints

Exploratory endpoints are analyzed up to end of randomized macitentan or SoC + 7 days.

- Panama FC status (I or II vs III or IV) at Week 24.
- Change from Baseline to Weeks 12, 24 and 48 in exercise capacity as measured by the 6MWT in children ≥ 6 years of age who are developmentally able to understand and perform the test.
- Percent of Baseline plasma NT-proBNP up to Week 48.
- Change from Baseline to Week 48 in number of hours of daytime activity assessed by accelerometry.
- Change from Baseline to Week 48 in mean count per minute of daily activity assessed by accelerometry.
- Change from Baseline to Week 48 in mean daily time spent in light physical activity based on a threshold from 800 to 3199 activity counts per minute assessed by accelerometry.

Baseline is the last non-missing value observed before or on the day of randomization/Visit 2.

## 6.2 Safety Endpoints

Safety endpoints are assessed until EOS and include:

- AEs and SAEs
- AEs leading to premature discontinuation of macitentan or SoC
- AEs of special interest
- Marked laboratory abnormalities

[1] This endpoint will be assessed by subjects and as assessed by a caregiver (e.g., parent) as described in Section 6.3.

- Change from Baseline in selected laboratory parameters [refer to Section 11.3.5.2] to all timepoints of assessments
- Change from Baseline in vital signs (BP, heart rate) to all timepoints of assessments
- Growth from Baseline to all timepoints of scheduled assessments
- Sexual maturation (Tanner stage) change from Baseline to all timepoints of scheduled assessments

Baseline is the last non-missing value observed before or on the day of randomization/ Visit 2.

Cohort of children < 2 y.o. will be summarized separately.

## 6.3 Other Quality of Life Endpoints

In English-speaking subjects in the USA, change from Baseline to all timepoints of assessments up to end of randomized macitentan or SoC + 7 days in:

- QoL as measured by the disease-specific PedsQL™ 3.0 Cardiac Module using the "heart problems and treatment" component only.
- QoL as measured by the PedsQL™ Multidimensional Fatigue Scale standard version using the "general fatigue" component only.

Each of these endpoints will be analyzed as assessed by subjects and as assessed by a caregiver (e.g., parent). Questionnaires are adapted for following age categories:

- Toddlers: 2 to 4 years of age
- Young children: 5 to 7 years of age
- Children: 8 to 12 years of age
- Adolescents: 13 to 18 years of age

For the youngest age category (toddlers) the questionnaire exists only for parent/caregiver (i.e., Parent Report). For all other age categories separate questionnaires exist for parent/caregiver and for subjects (i.e., Child report) and address the same items. For the cohort of children < 2 y.o., this questionnaire is not available.

## 6.4 Other Pharmacokinetic Endpoints

In a subpopulation of the macitentan arm or of those subjects in SoC who crossover to macitentan (up to 40 subjects ≥ 2 y.o. distributed over the different age groups) at steady-state for both macitentan and ACT-132577:

- PK profile over 24 hours at pre-dose and following administration of macitentan during steady-state conditions.

- The time to reach maximum plasma concentration ($t_{max}$) during a dosing interval.
- Maximum plasma concentration ($C_{max}$) during a dosing interval.
- The area under the plasma concentration-time curve during one dosing interval ($AUC_{\tau}$).

Plasma PK parameters of macitentan and ACT-132577 will be derived by noncompartmental analysis or population PK analysis of the plasma or blood concentration-time profiles.

The following assumptions have been made:

- $C_{max}$, AUC, and $t_{½}$ values are assumed to be log-normally distributed [Julious 2000].
- No period or carry-over effects.

The measured individual plasma concentrations of macitentan and ACT-132577 will be used to directly obtain $C_{max}$ and $t_{max}$.

$AUC_{\tau}$ will be calculated according to the linear trapezoidal rule using the measured concentration-time values above the limit of quantification (LOQ) during one dosing interval.

In subjects < 2 y.o. who are on macitentan, concentration of macitentan and ACT-132577 (aprocitentan) will be summarized per time point:

- PK assessment of single dose macitentan after the first dose (2, 5, and 24h) and trough concentrations at steady state.
- Collected PK data will be regularly assessed using non-linear mixed effects pharmacokinetic modeling during the course of the study to confirm the appropriateness of the selected dosing regimen in subjects < 2 y.o.

## 6.5 Drug formulation endpoint

The palatability and acceptability of the macitentan dispersible formulation after the first dose on Day 1 and at Week 12 (Visit 4) in subjects randomized to the macitentan arm.

# 7 STUDY ASSESSMENTS

All study assessments are performed by a qualified study personnel member: medical, nursing, or specialist technical personnel, and are recorded in the eCRF, unless otherwise specified. Assessments to be performed by a physician are specified in Section 3.3. If permitted by local legislation, physicians may delegate to an Advanced Practice Role (or an equivalent) specific tasks normally performed by a physician such as the consent

interview and the signature of the ICF without a second signature of a physician. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

Vital signs must be done before collection of blood sample. The study personnel is noting the time of those assessments in the source document. On days of PK sampling macitentan must not be administered to the subject before the pre-dose PK sample has been collected. The timing of PK sample collection is described in Section 7.7.1. At Visit 2 (Randomization) palatability and acceptability of macitentan is assessed after the subject has taken the first dose of macitentan. The order of the other assessments is not specified.

If the PI delegates any study procedure/assessment for a subject, e.g., echocardiography, blood sampling to an external facility, he/she must inform the Sponsor (or delegate) to whom these tasks are delegated. The set-up and oversight will be agreed upon with the Sponsor (or delegate). The supervision of any external facilities remains the responsibility of the PI.

Calibration certificates for the following equipment used to perform study assessments must be available prior to the screening of the first subject:

- Body weight scale
- Thermometers for study drug storage and blood sample storage (e.g., PK)
- Local laboratory certification and reference ranges
- Echocardiography machine

The calibration certificates must be filed in the Investigator Site File (ISF).

The ICF must be signed and dated before performing any study-mandated procedure. If the signing of ICF and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed (i.e., time of signatures and time of procedures will be documented). If a study-specific procedure or assessment has been performed as part of routine assessments and the results are available prior to the signing of the ICF, they may be used to assess eligibility and do not have to be repeated. In such cases, it must be clear from the source document when and for which reason the assessment was done prior to the signing of the informed consent.

The schedule of study assessments is provided in Table 1, Table 2, and Table 3 and in Section 8.

## 7.1 Screening/Baseline Assessments

For subjects with PAH with co-incidental CHD, i.e., small atrial septal defect, ventricular septal defect or patent ductus arteriosus which themselves do not account for the development of elevated PVR, the investigator submits relevant clinical, RHC and

echocardiography data to the BCAC for review and approval [see Section 3.4]. Only after BCAC confirms the diagnosis of PAH associated with co-incidental CHD will the subjects be randomized, provided all other entry criteria are confirmed.

### 7.1.1 Baseline Demographics

Baseline demographics include sex, ethnicity/race, age and weight/height (or length) and are recorded in the eCRF.

Clinically relevant medical history as defined in Section 4.6 is documented and recorded in the eCRF. The presence/absence of Down Syndrome is recorded for all subjects in the eCRF.

### 7.1.2 Baseline Disease Characteristics

Disease characteristics such as PAH etiology, PAH diagnosis (mPAP, PAWP [or LAP, or LVEDP], PVRi values assessed by RHC and date of diagnosis), and date of first observed/assumed PAH symptoms are documented and reported in the eCRF.

## 7.2 Previous/Concomitant Therapy

For reporting of medications and of PAH-related non-pharmacological interventions refer to Section 5.2.2.

## 7.3 Efficacy assessments

In order to assess endpoints related to disease progression, 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 [refer to Section 5.2.2].
- 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 5.2.2].
- For hospitalizations, the admission/discharge date together with the reason for hospitalization is recorded on either the AE eCRF page or on the dedicated clinical worsening eCRF page (if cause is related to PAH) as indicated in Section 8.9.
- 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 7.3.1.

The investigator (or delegate) will describe the condition of the subject at Baseline (i.e. 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 subject's condition. Narratives and local echocardiography reports [refer to Section 7.3.3] are sent to the CEC

Coordinator who will upload them into the Adjudication system [refer to Section 8.9]. Narratives and locally read echocardiography data are not collected in the eCRF.

### 7.3.1 Monitoring of Disease Progression

#### 7.3.1.1 *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.

The occurrence of a new or worsening sign/symptom is not reported as AEs 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 [refer to Section 8.9].

#### 7.3.1.2 *Functional Class*

The WHO FC [see Appendix 3] and the Panama FC [Appendix 4] are recorded in the eCRF. The Panama FC is tailored for children up to 16 years of age [Lammers 2011] and thus its assessment will discontinue in children > 16 years of age.

If there is worsening in the WHO FC refer to Section 8.9 for reporting of disease progression. Worsening in Panama FC does not classify for disease progression but the data will be provided to the CEC as supportive data.

### 7.3.2 NT-proBNP

The quantification of NT-proBNP plasma levels will be performed by the Central Laboratory [see contact details, page 3]. Central laboratory data will be automatically transferred from the Central Laboratory database to the clinical database.

The blood volume to be taken at each timepoint will be approximately 1.2 mL.

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.

### 7.3.3 Echocardiography

**Central Reading:** At least the following parameters will be assessed as described in the TOMORROW image acquisition guidelines: left ventricular eccentricity index and tricuspid annular plane systolic excursion (TAPSE). These data are analyzed centrally as per Independent Review Charter and transferred electronically to the clinical database. The investigator (or delegate) submits generated echocardiography data in digital format, together with a Data Transmittal Form to the Central Echocardiography CRO [see contact details, page 3] as instructed in the TOMORROW Site Operations Manual. The CRO conducting the central reading will also receive the clinical data necessary for the interpretation of the images such as body weight/height and heart rate.

**Local Reading:** An echocardiography (and/or Doppler) to document the severity of PAH (assessing, e.g., pericardial effusion, right ventricular pressure, inferior vena cava size) is performed as per local practice during Screening. The data are analyzed locally. In the presence of suspected disease progression, the same parameters are assessed as a follow-up echocardiography (and/or Doppler) in order to document whether there is any change since Baseline. The report of the Baseline and of the follow-up echocardiography at disease progression is sent to the CEC Coordinator who provides this as supportive data to the CEC [refer to Section 8.9].

In addition, for subjects with PAH with co-incidental shunts, the local echocardiography used to confirm eligibility must be submitted to the BCAC [see Sections 3.4 and 7.1].

### 7.3.4 Physical Activity

In subjects of at least 2 years of age, 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 subject is assessed via accelerometer in subjects of at least 2 years of age. The subject collects data wearing the accelerometer for 10-14 consecutive days before respective visits [refer to Table 1 or Section 8]. If, for any reason,

data are not collected before respective study visits, the subject will collect the data during the 10-14 days following the visit. This does not apply for the assessment during Screening. For Screening, the physical activity must be collected any time during Screening and before Visit 2. This will allow collecting data during week days and weekend days and will provide a reliable estimate of the usual physical activity of the subject.

At Visit 1 the investigator (or delegate) instructs parent(s) / legally designated representative and developmentally capable subjects on how and when to wear the accelerometer (refer to TOMORROW Accelerometry Guidelines). The accelerometer is worn during the waking hours of the subject. The device may be removed during the night rest and during activities when the device could get wet (e.g., showering, bathing, swimming).

The parent(s) / legally designated representative or subject bring the device to the study-site at site visits and the investigator (or delegate) transfers the data to the accelerometry Central Laboratory as instructed in the TOMORROW Accelerometry Guidelines. For subjects who are not eligible to participate in the study, data (if collected during Screening) is transferred to the central lab. At Visit 7 the accelerometer will not be returned to the subject. After successful data transfer the device is re-set and can be re-used by another study subject.

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 CRO.

Accelerometer devices will be provided to the investigational site before the start of the study.

### 7.3.5 6-minute walk test

The 6-minute walk test (6MWT) is a non-encouraged test that measures the distance covered by the subject during a 6-minute walk. Guidelines are provided in the TOMMOROW 6-Minute Walk Test Guidelines.

The 6-minute walk distance (6MWD) will be assessed in subjects ≥6 years of age who understand and are able to perform the test correctly [Douwes 2015, Takatsuki 2013b] and who can perform the test per protocol at randomization. Test results and the date and time of assessment will be recorded in the eCRF. If a subject wears a mask during the 6MWT this will be entered in the source document but not in the eCRF.

## 7.4 Safety Assessments

The definitions, reporting and follow-up of AEs, SAEs, and pregnancies are described in Section 10.

### 7.4.1 Vital Signs

Vital signs include systolic and diastolic BP and heart rate. Vital signs are measured non-invasively.

It is recommended that vital signs are measured after the subject has rested at least 5 minutes (e.g., sitting). If applicable, vital signs are measured before any invasive assessment (such as blood draw).

The same type of device is used throughout the study for an individual subject. In addition, throughout the study BP is measured on the same arm for an individual subject.

Vital signs are recorded in the eCRF.

### 7.4.2 Weight and Height/Length

Body weight and height/length are measured and recorded in the eCRF.

- For children less than 2 years of age length is measured while the child is lying down.
- For children above 2 years of age, height will be measured using a stadiometer.

### 7.4.3 Physical Examination

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. The observations should be reported according to body system in the eCRF as either normal or abnormal. If an abnormality is found it should be specified on the corresponding eCRF page (except for abnormalities related to PAH worsening), describing the signs related to the abnormality (e.g., fever, coughing, dyspnea) and not the diagnosis (e.g., pneumonia). 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 10.1.1], must be recorded on the AE page of the eCRF.

During the SAEP, the physical examination will only be documented in the subject's medical chart and not in the eCRF. Abnormal observations must be reported in the AE pages of the eCRF.

Signs and symptoms related to PAH are not reported together with the physical examination findings but on dedicated eCRF pages [refer to Section 7.3.1.1].

### 7.4.4 Tanner Stage

As per CHMP Paediatric addendum to the PAH guidelines [EMA/CHMP/213972/2010] sexual maturation of pediatric patients in long-term studies is of particular importance. Therefore the Tanner stage [refer to Appendix 5] is assessed at regular timepoints during the study.

Tanner stage is assessed in female subjects ≥ 8 years of age and in male subjects ≥ 9 years of age (i.e., examination is started once they are 8 and 9 years old, respectively). For subjects who enter the study below these ages sexual maturity assessments will start once they reach the ages of 8 or 9 years (for girls and boys, respectively). Tanner stage assessment is stopped once full sexual maturation is reached (if applicable before EOS). (Self-)Assessment of pubertal Tanner stage by parents or subjects may be allowed by the study investigator. In this case, the investigator instructs and assists parents / subjects on how this should be assessed at each time of scheduled assessment.

The Tanner stages of puberty in girls are based on breast size and shape and pubic hair distribution. The Tanner stages of puberty in boys are based on the development of the genitalia and pubic hair distribution [Blondell 1999, Marshall 1969, Marshall 1970]. Actual age at milestone attainment may vary among individuals and among different study populations.

In female subjects the investigator verifies at each study visit (including unscheduled visits) the childbearing potential of the subject [refer to Section 4.5.1].

The site study personnel will record the Tanner stage and the childbearing potential in the eCRF. For subjects with childbearing potential the study personnel will verify at each visit whether the subject has or plans to become sexually active. If confirmed the study personnel will counsel the subject on the appropriate methods of contraception [refer to Section 4.5.2].

### 7.4.5 Laboratory Assessments

#### 7.4.5.1 *Type of Laboratory*

A Central Laboratory (see Central Laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

Laboratory parameters at Visits 1 and 2 (Randomization) are assessed by the Central Laboratory.

Under specific circumstances (e.g., if the subject lives far from the site and cannot return every month), laboratory samples may be collected at a laboratory close to where the subject lives (local laboratory) and sent to the Central Laboratory for analysis. Alternatively and if allowed per local regulations, a study nurse (or study person qualified to collect blood samples) or a CRO can collect samples at subject's home and send them to the Central Laboratory for analysis.

In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency, or missing Central Laboratory values) valid local laboratory results, if available, will be entered into the clinical database together with the respective normal ranges via dedicated eCRF pages. For monthly liver and hemoglobin/hematocrit tests, a local laboratory may be used if normal ranges are available for the given age group of the subject. Respective local laboratory results will be entered into the eCRF together with the respective normal ranges.

In case a Central Laboratory sample is lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time-window and these test results are available.

Central laboratory reports will be sent to the investigator. In case of specific (predefined) laboratory abnormalities, the Central Laboratory will alert the CRO and the concerned site. Alert flags that will trigger such notifications are displayed in the Laboratory Manual.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings (local laboratory report) that are known at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant laboratory abnormalities (Central Laboratory or local laboratory) detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10], and must be followed until the value returns to within the normal range, or until the change is no longer clinically relevant. Further laboratory analyses should be performed as indicated and according to the judgment of the investigator.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the Laboratory Manual. Material required for sampling will be provided to the investigational site before the start of the study.

#### 7.4.5.2 *Laboratory Tests*

Assessment of plasma NT-proBNP is described in Section 7.3.2. For PK assessments refer to Section 7.7.

For the complete list of laboratory tests and their normal ranges refer to Laboratory Manual.

**Hematology**

Hemoglobin and hematocrit are assessed to confirm eligibility. Values must be available within 6 weeks prior to Visit 2 (Randomization). Local laboratory values may be used and recorded in the eCRF, if normal ranges applicable for the age category of the subject are available.

Complete hematology tests include:

- Hemoglobin,
- Hematocrit,
- Erythrocyte count,
- Leukocyte count with differential counts,
- Platelet count.

Hemoglobin must be monitored monthly in all subjects in the macitentan group for the first 6 months of study period and subsequently at each scheduled visit (every 12 weeks) until EOS. In the SoC group monthly tests are only mandatory for subjects receiving an ERA for which respective label instruction requests monthly tests. In all other subjects in the SoC group those tests are done at the regular study visits (i.e., every 12 weeks).

Subjects in the SoC group who cross over to macitentan after CEC-confirmed disease progression event or at entry into single arm extension period must have their hemoglobin and hematocrit levels assessed before macitentan is initiated, to confirm hemoglobin and/or hematocrit are ≥ 75% of the LLN [refer to Section 8.10 and Section 8.13]. If levels are lower, macitentan treatment start must be delayed until re-tests show hemoglobin and hematocrit levels are ≥ 75% of the LLN. These values must be monitored monthly for the first 6 months of macitentan treatment and every 12 weeks thereafter.

In the presence of decreased hemoglobin values refer to Section 5.1.10 for instructions regarding interruption of macitentan study treatment.

**Clinical chemistry**

Liver aminotransferases (AST and ALT), creatinine and creatinine clearance are assessed to confirm eligibility. Values must be available within 6 weeks prior to Visit 2 (Randomization). Local laboratory values may be used and recorded in the eCRF, if normal ranges applicable for the age category of the subject are available.

Complete blood chemistry tests include:

- Liver tests: aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin,
- Creatinine and creatinine clearance,
- Blood urea nitrogen,
- Glucose,
- Sodium,
- Potassium,
- Calcium.

In all subjects ≥ 2 y.o. in the macitentan group, liver tests must be monitored monthly for the first 6 months of study period and at each scheduled visit (every 12 weeks) until EOS.

In subjects of < 2 y.o., liver tests must be monitored monthly for the first 12 months of study period and at each scheduled visit (every 12 weeks) thereafter until EOS.

The investigator may decide to continue monthly liver test monitoring via central lab. This is not mandated per protocol; however liver tests are mandatory every 12 weeks. In the SoC group monthly liver tests are only mandatory for subjects receiving an ERA for which the respective label instruction requests monthly tests. In all other subjects in the SoC group those tests are done at the regular study visits (i.e., every 12 weeks).

Subjects in the SoC group who cross-over to macitentan after CEC-confirmed disease progression event or at entry into single arm extension period must have liver aminotransferase levels assessed before macitentan is initiated to confirm ALT and AST are ≤ 3 × ULN [refer to Section 8.10]. If levels are higher, macitentan treatment start must be delayed until re-tests show ALT and AST levels ≤ 3 × ULN. These values must be monitored monthly for the first 6 months of macitentan treatment and every 12 weeks thereafter.

In the presence of elevated AST/ALT values, refer to Section 5.1.10 for instructions regarding interruption of macitentan study treatment.

**Pregnancy test**

In both treatment arms female subjects of childbearing potential are monitored for pregnancy during Screening and until EOS or safety follow-up telephone call (whichever is last).

During screening, a serum pregnancy test will be done. At randomization, a urine pregnancy test will be performed and is verified by the investigator (or delegate).

Subjects who are sexually active and use hormonal contraception must have been receiving those medications at least 4 weeks before the pregnancy test at Visit 2 [refer to Section 5.2.3].

Macitentan study treatment must not start in female subjects of childbearing potential before results of the pregnancy test are available and negative.

Monthly monitoring of pregnancy is performed using urine pregnancy tests. The urine pregnancy test can be done via urine dipstick by the subject at home and under supervision of her parent(s)/caregiver/guardian until reaching legal age. Pregnancy tests approved as per local requirements will be provided to the respective subjects. The investigator (or delegate) will confirm via phone call that the test was done and will verify the results. If a urine pregnancy test is inconclusive a serum pregnancy test must be done.

If pregnancy is suspected during the study, a serum pregnancy test must be performed. If pregnancy is confirmed, macitentan must be stopped as per Section 5.1.10.

## 7.5 Palatability and Acceptability of Macitentan Drug Formulation

Subjects randomized to the macitentan group report the palatability and acceptability (separately) of the pediatric formulation.

Subjects aged 4 years and more will be instructed to rate the palatability and acceptability of the daily dose of dispersed macitentan by marking the appropriate face on a 5-point facial hedonic scale via a circle or a cross. For younger children the caregiver will be instructed to rate the ease to administer the daily dose of dispersed macitentan to the subject using the same 5-point facial hedonic scale [refer to Appendix 6]. For subjects who are developmentally not capable of reporting palatability and acceptability (e.g., subjects with Down Syndrome), the caregiver will complete the questionnaire. The investigator will judge whether a subject is capable to complete the palatability and acceptability questionnaire.

The site study personnel will record the score and the method of administration (e.g., spoon) in the eCRF.

## 7.6 Quality of Life Assessments

The QoL will be assessed for subjects of at least 2 years of age. Below that age the selected questionnaires are developmentally not appropriate and are thus not collected.

The PedsQL™ Pediatric Quality of Life Inventory version 4.0 short form (SF15) will assess the general physical, emotional, social and school functioning (15 questions) [refer to Appendix 7 :]. The “heart problems and treatment” component of the PedsQL™ Cardiac Module version 3.0 and the “general fatigue” component of the PedsQL™ Multidimensional Fatigue Scale standard version paper questionnaires assess:

- Heart problems and problems with treatment (7 questions) [Appendix 8], and
- Problems with general fatigue (6 questions) [Appendix 8]

The questionnaires are adapted for different age groups: toddlers (2-4 years of age), young children (5-7 years of age), children (8-12 years of age) and adolescents (13-18 years of age).

For toddlers a parent or caregiver completes the QoL questionnaire and rates each item using a 5-point Likert scale per item. For young children (excluding toddlers) a site study person reads the questions to the subject and asks the child to point to a 3-scale smiley score (Young Child Report). This score is then marked by the site study person. In older age groups subjects complete their age-adapted QoL questionnaire using a 5-point Likert scale for each item. A parent/caregiver additionally completes the QoL questionnaire (Parent Report) adapted to rate their young child, child or adolescent also using a 5-point Likert scale per item. For subjects growing into adults (reaching legal age) Parent Reports will not be collected. For subjects with Down Syndrome only Parent Reports are collected. Subjects and parent(s)/caregiver(s) are asked to rate the QoL considering the 1-month period preceding the completion of the questionnaire.

The QoL paper questionnaire is completed by parent(s)/caregiver(s) and by subjects. The cardiac and fatigue components will only be assessed for English-speaking subjects in the USA, since these questionnaires have only been validated for the USA.

- The Parent Report (QoL questionnaire) will preferably be completed by the same parent/caregiver at all timepoints for an individual subject. If the parent cannot visit the site at the time when the QoL questionnaire must be completed, the parent can complete it at home within a planned period of the scheduled visit, sign and date the original form and return it to the site.
- If the subject changes age group during the conduct of the study, the same questionnaire as at Visit 2 will be continued.
- Parent(s)/caregiver(s) and subjects who complete the questionnaire sign the paper questionnaire.
- For young children the study person who (together with the subject) completed the Young Child Report signs the questionnaire.

The site study personnel will record the QoL scores from parent(s)/caregiver(s) and subjects into the eCRF. The reason for missing data are recorded by the investigator or delegate in the eCRF.

For the data analysis the 5-point Likert scale (from 0 [never] to 4 [almost always]) will be reversed, scored, and linearly transformed to a 0  100 scale as follows:

0  100, 1  75, 2  50, 3  25, 4  0.

All items have the same weight. If more than 50% of the items in the scale are missing, the scale scores will not be computed.

## 7.7 Pharmacokinetic Assessments

Macitentan and its active metabolite ACT-132577 will be determined in plasma and blood samples. Samples will not be used for any genomic screening.

### 7.7.1 Timing for PK Sampling

In all subjects who are 2 y.o. and older randomized to macitentan and receiving macitentan, a trough sample (i.e., pre-dose) will be drawn on Visit 4 (Week 12) for PK assessments.

In addition, up to 40 subjects (distributed over the different age groups) receiving macitentan study treatment (randomized or after cross-over), a PK profile will be collected. At Visit 3, the blood samples for the PK profiling must be drawn at the following timepoints: Immediately before administration of the dose of macitentan study treatment (pre-dose) and then 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h (before macitentan intake the next day) post-dose.

In subjects younger than 2 y.o., samples will be drawn at 2h, 5h, and 24h after the first macitentan dose at Visit 2. Trough samples (i.e., pre-dose) will be drawn on Week 4 and 8 (refer to Section 7.7.2).

### 7.7.2 Procedures for Sampling

Approximately 0.5 mL of blood per time point will be collected in tubes containing ethylene diamine K3 tetra-acetic acid.

For children < 2 y.o., in addition, a volume of approximately 40 µL of blood will be collected at each timepoint using Neoteryx Mitra™ samplers (resulting in dried blood samples) where the use of this sampler is allowed per local requirements. Based on emerging data, method for PK sampling in children < 2 years of age may be switched to 0.5 mL blood sampling per time point only or dried blood sampling via Neoteryx Mitra™ samplers only.

Details for sample collection, labeling and shipping will be described in the laboratory manual. The date and exact actual clock time of each blood sample draw will be entered into the eCRF. In addition, the last dosing date and time of macitentan intake before and after blood PK sampling will be collected in the eCRF.

### 7.7.3 Bioanalysis

The concentrations of macitentan and its metabolite ACT-132577 in plasma from PK samples and in dried blood (for children < 2 y.o.) will be determined using validated liquid chromatography coupled to mass spectrometry methods, by or under supervision of the sponsor.

### 7.7.4 3-Total Blood Volume

For subjects ≥ 2 y.o., the total blood volume drawn for the PK assessments will be approximately 0.5 mL at steady state with an additional 7×0.5 mL 3.5 mL for the subjects that participate in the PK substudy.

For subjects < 2 y.o., the total volume drawn for PK assessments will be approximately 1.7 mL at Visit 2 and approximately 0.6 mL at steady state (Week 4 and Week 8) .

## 8 SCHEDULE OF VISITS

To ensure compliance, at each visit, the study personnel must verify with female subjects of childbearing potential whether they are sexually active and must remind those who are sexually active to use the methods of contraception defined for this study. The reminders must be documented in the subject chart.

Unscheduled visits may be performed at any time during the study. During an unscheduled visit, assessments to verify worsening of PAH (until EOCP) and presence of AEs/SAEs must be performed [see Table 1, Table 2, Table 3 and Section 8.11]. In addition, depending on the reason for the unscheduled visit (e.g., an AE), appropriate assessments will be performed based on the judgment of the investigator and the results 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. During the SAEP, unscheduled visits are not recorded in the eCRF but (S)AE are reported, if applicable.

To minimize pain and distress an anesthetic cream (e.g., EMLA® cream containing lidocaine 2.5% and prilocaine 2.5%) may be applied prior to any venipuncture as per preference of the subject or parent(s)/caregiver. Local anesthetics will be recorded as concomitant medications in the eCRF.

### 8.1 Screening / Visit 1

The screening period can take up to 6 weeks and ends with randomization or screening failure. It can comprise several site visits. However, for simplicity this will be referred to as Visit 1 for all subjects.

For the cohort of children < 2 y.o., screening ends with confirmation of eligibility and assignment of macitentan kit at Visit 2, or with screening failure.

Once the subject's parent(s) / legally designated representative have signed the ICF and assent has been obtained from developmentally capable subjects the investigator enrolls the subject into the study through the IRT system which will provide a unique subject number. The investigator documents the planned SoC in the IRT system for subjects ≥ 2 y.o.

For subjects with co-incidental CHD the investigator submits data to the BCAC [refer to Sections 3.4 and 7.1]. Only after BCAC confirms the eligibility, the investigator randomizes the subject given all other entry criteria are confirmed.

If eligibility of a subject cannot be confirmed within the 6-weeks Screening period, it is permitted to re-screen the subject once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient washout period of a forbidden medication). All screening assessments should then be repeated at the time of re-screening and are used to randomize the subject in IRT (if eligible) using the same subject number.

Visit 1 includes:

- Informed consent from parent(s) / legally designated representative and assent from developmentally capable subjects
- Verification PAH diagnosis

And assessment of:

- Demography and medical history
- Baseline disease characteristics (co-incidental CHD requires approval through BCAC)
- Previous and concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH
- WHO FC and Panama FC
- Echocardiography
- Physical activity (collected anytime during Screening and before Visit 2)
- 6MWT
- Vital signs (BP, heart rate)
- Weight and height/length
- Physical examination
- Laboratory tests (complete hematology and clinical chemistry)
- Tanner stage
- Serum pregnancy test in subject of childbearing potential (SOCBP)
- AE/SAE

Some of these assessments depend on the age of the subject, please refer to Section 7 and to Table 1 and Table 2. Study assessments can be distributed over the entire screening period. At Visit 1 the investigator (or delegate) instructs parent(s) / legally designated representative and developmentally capable subjects on how and when to wear the accelerometer [refer to Section 7.3.4]. Furthermore, for female subjects of childbearing potential and who are sexually active, the investigator discusses methods of contraception.

At Visit 1, 3 mL of blood is collected for hematology and clinical chemistry. In addition, in SOCBP (and including those subjects who had tubal sterilization), 1 mL of blood is collected to exclude pregnancy. Routine test results may be used as specified in Section 7.4.5.

## 8.2 Randomization / Visit 2 (Day 1)

The investigator will verify all inclusion and exclusion criteria assessed during Screening and will decide on the final eligibility of the subject. The investigator marks the source data used to assess subject's eligibility. For potential re-screening refer to Section 8.1.

Visit 2 includes assessment of:

- Vital signs (BP, heart rate) [#]
- Previous and concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH
- WHO FC and Panama FC
- 6MWT
- Plasma NT-proBNP[#]
- Weight[#] and height/length
- Physical examination[#]
- Laboratory tests (complete hematology and clinical chemistry) [#] unless blood sample at Visit 1 (Central Laboratory) was collected within 1 week before Visit 2
- For children < 2 y.o.: PK samples at 2h, 5h, and 24h after the first macitentan dose
- Urine pregnancy test in SOCBP[#]*
- QoL
- AE/SAE

Some of these assessments depend on the age of the subject, please refer to Section 7 and to Table 1 and Table 2. All assessments will be done on the same calendar day. The QoL questionnaire may be reported within ±5 calendar days of the visit. The investigator, based on the assessments above and any other relevant information in the medical chart, will write a Subject Narrative, which will help as a reference at the time of a disease progression.

[#] These assessments must be done **before randomization** (and for children < 2 y.o. before first dose of macitentan study drug).

* Subjects who are sexually active and who use hormonal contraceptives must have initiated those medications at least 4 weeks prior to the test at Visit 2 [refer to Section 4.5.2].

At Visit 2, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology and clinical chemistry. For subjects < 2 y.o., approximately 1.7 mL is additionally taken for

PK. In addition in SOCBP (and including those subjects who had tubal sterilization) urine is collected to exclude pregnancy. Routine test results may be used as specified in Section 7.4.5.

If a subject is not eligible, the reason for screening failure will be entered in the eCRF. Baseline data collected until confirmation of Screening failure are also recorded in the eCRF. If Baseline data are available from any Central Laboratory (e.g., physical activity) those will be transferred to the clinical database.

For subjects ≥ 2 y.o. at Visit 2: If the eligibility of the subject is confirmed, the investigator performs or oversees:

- Documentation of SoC (including ERA: yes vs no) and WHO FC (FC I/II vs FC III) in the IRT system
- Randomization through IRT (subjects taking ERAs are limited up to 40% of the overall number of randomized subjects).

In subjects randomized to macitentan, and in subjects < 2 y.o., Visit 2 also includes:

- Macitentan study treatment dispensing
- Palatability and acceptability of macitentan

In subjects randomized to SoC, the investigator

- Prescribes SoC as documented in the IRT

For subjects randomized to the macitentan group, the subject's body weight recorded at Visit 2 will be used by the IRT system to calculate the daily dose of macitentan [refer to Table 6 and Table 7] and to assign the respective study treatment kit. For subjects < 2 y.o., age will be used by IRT system to calculate the daily dose of macitentan.

The study personnel instructs parent(s) / legally designated representative and developmentally capable subjects on macitentan administration [refer to Section 5.1.5]. In SOCBP (and including those subjects who had tubal sterilization) macitentan study treatment can only be started in the presence of a negative pregnancy test. For subjects randomized to SoC PAH-specific medications are continued or newly initiated as instructed in Section 5.1.2.

For subjects < 2 years of age at Visit 2:

For PK assessment, approximately 1.7 mL of blood (including dried blood samples via Neoteryx Mitra™ device where the use of this sampler is allowed per local requirements) are collected at 3 timepoints after the first dose of macitentan as described in Section 7.7.1.

## 8.3 PK Visits at Week 4 and Week 8 for Subjects < 2 y.o.

This visits apply only to cohort < 2 years of age at first dose of macitentan study treatment. The visit will take place at steady-state conditions for macitentan and its active metabolite (ACT-132577), i.e., subjects must have received at least 10 days of continuous administration of the same dose of macitentan. For subjects who prematurely discontinue macitentan treatment before the planned visit(s), the respective visit(s) will be cancelled.

Parent(s) / legally designated representative must be reminded before Week 4 and before Week 8 visits not to administer macitentan before blood has been collected for the PK sampling and for laboratory safety tests on the day of the Visits but to bring the macitentan to the site for administration.

During these visits the following is collected and reported:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and Symptoms of PAH[#]
- Weight and height/length
- Physical examination
- Laboratory tests (hemoglobin, hematocrit and liver tests)
- PK sample
- AE/SAE

The assessments are done on the same calendar day. Approximately 0.5 mL of blood and a dried blood sample via Neoteryx Mitra™ device (where allowed) are collected to assess trough (pre-dose) PK. In addition, 2 mL of blood is collected to assess hemoglobin/ hematocrit and liver tests.

The daily macitentan dose is taken at site after the collection of the PK samples.
The investigator (or delegate) will document the date, time, and dose of macitentan before and after PK sample collection as well as the date and time of the PK sample (blood collection).

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.4 PK Substudy / Visit 3 for Subjects ≥ 2 y.o. on Macitentan/ Visit 3

This visit applies only to subjects ≥ 2 y.o. receiving macitentan and who signed the informed consent for the PK substudy [refer to PK substudy in Section 3.1] or to subjects randomized to SoC and crossing over to macitentan and providing informed consent for the PK substudy during the Cross-over visit. The visit will take place at steady-state conditions for macitentan and its active metabolite (ACT-132577), i.e., subjects must have

received at least 10 days of continuous administration of the same dose of macitentan. To collect the PK profile, it is recommended that the subjects stay overnight in the investigational site. This is, however, not mandated. The investigator will instruct subjects who leave the hospital that some medications are forbidden due to drug-drug interactions with macitentan, and not to take the next macitentan dose until after the last PK sample is taken the next morning. For subjects who prematurely discontinue macitentan treatment before the planned Visit 3, the visit is cancelled.

Parent(s) / legally designated representative must be reminded before Visit 3 not to administer macitentan before blood has been collected for the pre-dose PK sampling on the day of Visit 3, and not to administer macitentan the next morning before the last PK sample is drawn.

Visit 3 includes collection and reporting of:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and Symptoms of PAH[#]
- Weight and height/length
- Physical examination
- Laboratory tests (complete hematology and clinical chemistry)
- PK samples for PK profile
- AE/SAE

The assessments are done on the same calendar day the first PK sample is collected. At Visit 3, 3.5 mL of blood is collected to assess PK profile. In addition, 3 mL of blood is collected to assess hematology and clinical chemistry.

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.5 Treatment Visits / Visit 4 (Week 12)

Visit 4 occurs 12 weeks (± 2 weeks) after randomization. Parent(s) / legally designated representative of subjects ≥ 2 y.o. must be reminded before Visit 4 that macitentan study treatment should not be administered at the day of Visit 4 until after blood has been collected for PK sampling. The subject's body weight is verified by the investigator to adjust the study treatment dose of macitentan as appropriate [refer to Section 5.1.5]. For subject < 2 y.o. the age is verified for correct macitentan dose.

The investigator discusses monthly hemoglobin, liver test results with the parent(s) / legally designated representative as appropriate and verifies that monthly urine pregnancy tests, if applicable, have been performed and were negative. The investigator also assesses whether

a subject has reached childbearing potential and, if confirmed, whether the subject is sexually active to ensure counseling for appropriate contraception.

Visit 4 includes assessment and reporting of:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Plasma NT-proBNP
- Echocardiography
- Physical activity
- 6MWT (for subjects who performed this test at Visit 2)
- Weight and height/length
- Physical examination
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test (in SOCBP)
- Palatability and acceptability of macitentan[§]
- QoL
- PK trough sample[§]
- AE/SAE

Visit 4 also includes:

- Macitentan study treatment dispensing/return

Some of these assessments depend on the age of the subject, please refer to Section 7 and to Table 1 and Table 2. The blood samples for NT-proBNP and PK trough are collected on the same calendar day. The other assessments should preferably be done on the same calendar day but if necessary can be done within ±5 calendar days. The physical activity is not assessed at site but is collected by the subject via accelerometry device. At Visit 4, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology and clinical chemistry. In subjects ≥ 2 y.o. treated with macitentan, 0.5 mL of blood is collected for PK. In addition in SOCBP (including subjects with tubal sterilization) urine is collected to exclude pregnancy.

[#] In the presence of clinical worsening, refer to Section 8.9.
[§] In subjects treated with macitentan.

## 8.6 Treatment Visits / Visit 5 (Week 24)

Visit 5 occurs 24 weeks (± 2 weeks) after randomization. The investigator discusses monthly hemoglobin, liver test results with the parent(s) / legally designated representative as appropriate and verifies that monthly urine pregnancy tests if applicable have been performed and were negative. The investigator also assesses whether a subject has reached childbearing potential and if confirmed whether the subject is sexually active to ensure counseling for appropriate contraception. Furthermore the investigator reminds parent(s)/ legally designated representative that monthly monitoring of hemoglobin and AST/ALT is discontinued and that monthly urine pregnancy tests if applicable would continue.

Visit 5 includes assessment and reporting of:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Plasma NT-proBNP
- Echocardiography
- Physical activity
- 6MWT (for subjects who performed this test at Visit 2)
- Weight and height/length
- Physical examination
- Tanner stage
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test in SOCBP
- QoL
- AE/SAE

Visit 5 also includes:

- Macitentan study treatment dispensing/return

Some of these assessments depend on the age of the subject, please refer to Section 7 and to Table 1 and Table 2. Assessments should preferably be done on the same calendar day but if necessary can be done within ±5 calendar days of the visit day. The physical activity is not assessed at site but is collected by the subject via accelerometry device. The subject's body weight (or age for children < 2 y.o.) is verified by the investigator to adjust the study treatment dose of macitentan as appropriate [refer to Section 5.1.5].

At Visit 5, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology and clinical chemistry. In addition in SOCBP (including subjects with tubal sterilization) urine is collected to exclude pregnancy.

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.7 Treatment Visits / Visit 6 (Week 36), Visit 7 (Week 48)

Visits 6 and 7 occur 36 and 48 weeks (± 2 weeks) after randomization, respectively. The investigator verifies that monthly urine pregnancy tests, if applicable, have been performed and were negative. The investigator also assesses whether a subject has reached childbearing potential and, if confirmed, whether the subject is sexually active to ensure counseling for appropriate contraception.

Visits 6 and 7 include assessment and reporting of:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Plasma NT-proBNP
- Physical activity (before Visit 7)
- 6MWT (at Visit 7 for subjects who performed this test at Visit 2)
- Weight and height/length
- Physical examination
- Tanner stage (at Visit 7)
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test in SOCBP
- QoL (at Visit 7)
- AE/SAE

Visits 6 and 7 also include:

- Macitentan study treatment dispensing/return

Some of these assessments depend on the age of the subject, please refer to Section 7 and to Table 1 and Table 2. Assessments should preferably be done on the same calendar day but if necessary can be done within ±5 calendar days of the visit day. The physical activity is not assessed at site but is collected by the subject via accelerometry device. The subject's body weight (or age for children < 2 y.o.) is verified by the investigator to adjust the study treatment dose of macitentan as appropriate [refer to Section 5.1.5].

At Visits 6 and 7, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology and clinical chemistry. In addition in SOCBP (including subjects with tubal sterilization) urine is collected to exclude pregnancy.

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.8 Treatment Visits / Visit 8 (Week 60), Visit 9 (Week 72), etc.

Visits 8, 9 and subsequent treatment visits occur every 12 weeks (± 2 weeks), yearly visits (i.e., Visit 11, Visit 15, Visit 19, etc) every 48 weeks (± 2 weeks). The investigator verifies at each visit that monthly urine pregnancy tests if applicable have been performed and were negative. The investigator also assesses whether a subject has reached childbearing potential and, if confirmed, whether the subject is sexually active to ensure counseling for appropriate contraception.

Visits 8, 9, etc, include assessment and reporting of:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Plasma NT-proBNP
- Weight and height/length
- Physical examination
- Tanner stage (only every 6 months at Visits 9, 11, 13, etc)
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test in SOCBP
- QoL (only yearly, i.e., at Visits 11, 15, 19, etc)
- AE/SAE

Visits 8, 9, etc, also include:

- Macitentan study treatment dispensing/return

Assessments should preferably be done on the same calendar day but if necessary can be done within ±5 calendar days of the visit day. The subject's body weight is verified by the investigator to adjust the study treatment dose of macitentan as appropriate [refer to Section 5.1.5].

At Visits 8, 9, etc, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology and clinical chemistry. In addition in SOCBP (including subjects with tubal sterilization) urine is collected to exclude pregnancy.

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.9 Visit for a Disease Progression Event

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

During the Core Period, in the presence of suspected disease progression event (e.g., signs/symptoms denoting PAH worsening or deterioration of WHO FC [refer to Sections 7.3.1.1 and 7.3.1.2]), the investigator determines the main and contributing causes for worsening as per local practice. If applicable, the investigator reports which components of the disease progression 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"). **The disease progression event (i.e., 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 (e.g., 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 form.

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

The following assessments are performed and reported by the investigator in the eCRF:

- Vital signs
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological intervention
- Signs/symptoms of PAH
- WHO FC and Panama FC
- 6MWT (for subjects who performed this test at Visit 2)
- Main and contributing cause(s) of worsening
- Plasma NT-proBNP
- Physical examination
- QoL
- AE/SAE

In addition the following assessments/reports are done and provided by the investigator for uploading in the CEC adjudication system:

- Echocardiography report (locally read).

- Subject narrative describing the suspected disease progression event based on the assessments above and any additional relevant information in the medical chart to help the CEC committee to confirm the suspected event as a per protocol disease progression. In this endeavor, the investigator will use as Baseline reference the Subject Narrative written at Visit 2.

Assessments should preferably be done on the same calendar day but, if necessary, can be done within ± 5 calendar days of the visit day. At disease progression, 1.2 mL of blood is collected to assess plasma NT-proBNP.

In case the subject is hospitalized at another center than the investigational site, the investigator collects above data as available by contacting the treating center and requests the hospital discharge summary and the autopsy report (if applicable) and reports disease progression in the eCRF as best as possible, e.g., QoL, may in this case not be collected.

The investigator or delegate sends narratives (subject condition at Baseline and at disease progression) and a copy of the Baseline and follow-up echocardiography report as well as other relevant reports (such as hospital discharge letter, RHC report, etc) that support disease progression via email to the CEC Coordinator (see contact details in the ISF). The CEC Coordinator provides reports and narratives to the CEC as supportive data to assess disease progression. The CEC Coordinator ensures these are translated into English if provided in another language. The CEC Coordinator must ensure that narratives and copies of source data are blinded for subject identifiers (such as initials, birth dates, address, telephone numbers, etc [refer to Section 12.2]), and do not reveal the study treatment (macitentan versus SoC), the investigational site or country.

If the CEC requests further data or clarification (e.g., follow-up narrative), the CEC Coordinator will contact the respective investigator and forward the additional information to the CEC, if available. For further details regarding the role of the CEC refer to Sections 3.4 and 6.1.1 and to the CEC Charter.

If the CEC confirms the disease progression event, macitentan treatment will continue for subjects randomized to macitentan. For subjects randomized to SoC, macitentan will be offered if the investigator considers this to be in the best interest of the subject, and if the subject meets the qualifications to start macitentan treatment [refer to Section 8.10].

In all study subjects, assessment and reporting of any further disease progression continues until EOCP. All disease progression events reported until EOCP are adjudicated by the CEC.

## 8.10 Cross-over Visit

This visit applies only to subjects in the SoC group who have CEC-confirmed disease progression and who wish to cross-over to macitentan treatment. It is the investigator's responsibility to assess whether it is in the subject's best interest to cross over to macitentan, in particular for those subjects who are already on an alternative ERA treatment. Before macitentan treatment is started, the investigator must confirm the following to ensure the subject is eligible to start macitentan treatment:

1. Informed consent from subjects of legal age or informed consent to cross over is available from parent(s) / legally designated representative (assent from developmentally capable subjects ≥12 years of age)
2. Serum AST and/or ALT must be ≤ 3 × ULN (assessed by local or Central Laboratory within 6 weeks before or at the Cross-over Visit)
3. Severe hepatic impairment, e.g., Child-Pugh Class C [see Appendix 1] Note: Child Pugh Score must be fully documented for subjects with hepatic impairment as part of their medical history and/or clinical signs and evidence of hepatic impairment.
4. Hemoglobin or hematocrit must be ≥ 75% of the LLN (assessed by local or Central Laboratory within 6 weeks before or at the Cross-over Visit)
5. Renal function must not be severely impaired (i.e. estimated creatinine clearance ≥ 30 mL/min or serum creatinine ≤ 221 µmol/L)
6. In SOCBPs, pregnancy must be excluded via urine test
7. SOCBPs who are sexually active must use a reliable method of contraception (refer to Section 4.5.2)
8. No treatment with strong inducers of CYP3A4 within 4 weeks before Cross-over Visit (for list of medications, refer to exclusion criterion #11 in Section 4.4).
9. No systemic treatment with strong inhibitors of CYP3A4 nor with moderate dual CYP3A4/CYP2C9 inhibitors, or combination of a moderate CYP3A4 and a moderate CYP2C9 inhibitor within 4 weeks before Cross-over Visit (for list of medications, refer to exclusion criterion #12 and #13 in Section 4.4).

In addition, the following assessments are mandated during the same Cross-over visit and recorded in the eCRF:

- Vital signs (BP, heart rate)
- Weight and height/length
- Physical examination

- AE/SAE
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH
- WHO FC and Panama FC
- Plasma NT-proBNP (assessed by the Central Laboratory)*
- Laboratory tests (complete hematology and clinical chemistry assessed by the Central Laboratory)*

* Not mandated for subjects who are not eligible to start macitentan treatment.

Assessments should preferably be done on the same calendar day but if necessary can be done within ± 5 calendar days of the visit day.

If the subject is not eligible to start macitentan treatment the reason needs to be documented in the eCRF and the subject can be re-tested once for eligibility to start macitentan. In this case a new Cross-over Visit has to be scheduled and all eligibility criteria and assessments have to be reported again.

If the subject is eligible to start macitentan, the subject's body weight is entered by the investigator in IRT to calculate the daily dose of macitentan [refer to Table 6 and Table 7] and to assign the appropriate macitentan treatment kit [refer to Section 5.1.3]. The investigator (or delegate) dispenses the macitentan treatment and instructs parent(s) / legally designated representative and developmentally capable subjects on macitentan administration [refer to Section 5.1.5].

The investigator may also discuss potential participation of the subject in the PK substudy. A new optional informed consent/ assent is needed for subjects who cross-over to macitentan and who would like to participate in the PK substudy.

For subjects who cross-over to macitentan treatment, "end of standard of care" must be reported in the eCRF.

For subjects who cross-over to macitentan and who discontinue macitentan before End of Study the EOM visit and the safety follow-up call must be performed [refer to Sections 8.12 and 8.16].

## 8.11 Unscheduled Visits

Unscheduled Visits may occur at any time during study participation. During the Core Period, the investigator verifies that monthly urine pregnancy tests, if applicable, have been performed and were negative. The investigator also assesses whether a subject has reached childbearing potential and, if confirmed, whether the subject is sexually active to ensure counseling for appropriate contraception.

At an unscheduled visit during Core Period, the following assessments are mandated and recorded in the eCRF:

- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Physical examination
- Laboratory re-tests if applicable
- AE/SAE

Assessments should preferably be done on the same calendar day but, if necessary, can be done within ±5 calendar days of the visit day. Any other efficacy assessment [Section 7.3] or any safety assessment [Section 7.4] if collected are also recorded in the eCRF.

During the SAEP, the only data collected and reported as part of an unscheduled visit are (S)AEs and if applicable laboratory re-tests as requested in Section 5.1.10.

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.12 End of Macitentan (EOM)

If macitentan is prematurely discontinued, the subject must come for a site visit within 1 week after the last dose.

The investigator verifies that monthly urine pregnancy tests if applicable have been performed and were negative. The investigator also assesses whether a subject has reached childbearing potential and if confirmed whether the subject is sexually active to ensure counseling for appropriate contraception (which must continue until EOS), refer to Section 9.4.

The EOM visit includes:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Plasma NT-proBNP
- Weight and height/length
- Physical examination
- Tanner stage
- Laboratory tests (complete hematology and clinical chemistry)

- AE/SAE
- Macitentan study treatment return

Assessments should preferably be done on the same calendar day but, if necessary, can be done within ±5 calendar days of the visit day. Any other efficacy assessment [Section 7.3] or any safety assessment [Section 7.4] if collected are also recorded in the eCRF.

At EOM, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology, and clinical chemistry.

[#] In the presence of clinical worsening, refer to Section 8.9.

## 8.13 End of Core Period (EOCP)

Once clinical cut-off date for Analysis 2 is announced, individual EOCP visits are scheduled within 12 weeks.

The EOCP Visit includes:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological interventions
- Signs and symptoms of PAH[#]
- WHO FC and Panama FC[#]
- Plasma NT-proBNP
- Weight and height/length
- Physical examination
- Tanner stage
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test in SOCBP
- QoL
- AE/SAE

The EOCP Visit also includes:

- Macitentan study treatment dispensing/ return

Some of these assessments depend on the age of the subject, please refer to Section 7 and to Table 1 and Table 2. Assessments should preferably be done on the same calendar day but, if necessary, can be done within ± 5 calendar days of the visit day. At EOCP, 4.2 mL of blood is collected to assess plasma NT-proBNP, hematology and clinical chemistry. In addition in SOCBP (including subjects with tubal sterilization) urine is collected to exclude pregnancy.

At EOCP, participation to the SAEP will be proposed to eligible subjects.

For definition of EOCP for subjects who withdraw from the study or prematurely discontinue study visits, refer to Sections 8.17 and 9.2.

Eligibility for entering the SAEP with macitentan:

Before macitentan treatment is continued/started, the investigator must confirm the following to ensure the subject is eligible to enter the SAEP and continue/receive macitentan treatment:

1. Informed consent from subjects of legal age or informed consent to enter the SAEP is available from parent(s) / legally designated representative (assent from developmentally capable subjects ≥ 12 years of age)
2. Serum AST and/or ALT must be ≤ 3 × ULN (assessed by local or Central Laboratory within 6 weeks before or at the EOCP Visit)
3. Severe hepatic impairment, e.g., Child-Pugh Class C [see Appendix 1] Note: Child Pugh Score must be fully documented for subjects with hepatic impairment as part of their medical history and/or clinical signs and evidence of hepatic impairment
4. Hemoglobin or hematocrit must be ≥ 75% of the LLN (assessed by local or Central Laboratory within 6 weeks before or at the EOCP Visit)
5. Renal function must not be severely impaired (i.e. estimated creatinine clearance ≥30 mL/min or serum creatinine ≤ 221 µmol/L) (assessed by local or Central Laboratory within 6 weeks before or at the EOCP Visit)
6. In SOCBPs, pregnancy must be excluded via urine test
7. SOCBPs who are sexually active must use a reliable method of contraception (refer to Section 4.5.2) and agree to continue monthly urine pregnancy tests
8. No treatment with strong inducers of CYP3A4 within 4 weeks before EOCP Visit (for list of medications, refer to exclusion criterion #11 in Section 4.4).
9. No systemic treatment with strong inhibitors of CYP3A4 nor with moderate dual CYP3A4/CYP2C9 inhibitors, or combination of a moderate CYP3A4 and a moderate CYP2C9 inhibitor within 4 weeks before Cross-over Visit (for list of medications, refer to exclusion criterion #12 and #13 in Section 4.4).

[#] In the presence of clinical worsening refer to Section 8.9.

## 8.14 Single-arm Extension Period (SAEP)

Once subject is enrolled in the SAEP, individual Extension Visits are scheduled every 24 weeks (± 2 weeks).

The Extension Visit includes:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- Weight and height/length
- Physical examination
- Tanner stage
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test in SOCBP
- AE/SAE

The Extension Visit also includes:

- Macitentan study treatment dispensing/ return

## 8.15 End of Study

Once Study Closure is announced, individual EOS visits are scheduled within approximately 12 weeks.

The EOS Visit includes:

- Vital signs (BP, heart rate)
- Concomitant medications (including contraceptives)
- Weight and height/length
- Physical examination
- Tanner stage
- Laboratory tests (complete hematology and clinical chemistry)
- Urine pregnancy test in SOCBP
- AE/SAE

The EOS visit also includes:

- Macitentan study treatment return

Assessments should preferably be done on the same calendar day but, if necessary, can be done within ±5 calendar days of the visit day. At EOS, 3 mL of blood is collected to assess hematology and clinical chemistry. In addition in SOCBP (including subjects with tubal sterilization) urine is collected to exclude pregnancy.

At EOS (Study Closure) participation to a PTA or LTE study will be offered to subjects who otherwise have no access to macitentan or alternative treatment [refer to Section 3.1].

For definition of EOS for subjects who withdraw from the study or prematurely discontinue study visits, refer to Section 3.1.

## 8.16 Safety follow-up

For subjects who prematurely discontinue macitentan or SoC treatment the investigator will do the Safety FU 30 days (+ 1 week) after end of treatment. End of SoC will be declared, if a planned PAH-specific drug class is discontinued or if any additional PAH-specific drug class is added, or if the subject crosses over to macitentan after a CEC-confirmed disease progression event.

For subjects who continue study treatment until EOS and who do not enter any PTA or LTE study by Janssen, the investigator will do the Safety FU 30 days (+ 1 week) after EOS.

Subjects who continue study treatment until EOS and enter a Janssen PTA or LTE study will have no Safety FU call since they will be continuously followed in the Janssen PTA or LTE study.

The safety follow-up is conducted by the investigator through a telephone contact with the subject's parent(s) / legally designated representative or with subjects who came of legal age and includes assessment of:

- Information regarding urine pregnancy test in female subjects of childbearing potential (including subjects with tubal sterilization)
- AE/SAE

## 8.17 Survival Follow-up

Subjects for whom parent(s) / legal representative have withdrawn the consent to continue the planned schedule of assessments (regular study visits) but who are not withdrawn from the study [see Section 9.2] are contacted at least yearly by the study investigator and within 6 weeks before cutoff date for Analysis 1 and Analysis 2.

The last survival follow-up contact is performed for Analysis 2 and is considered EOS.

The survival follow-up contact includes assessment of:

- PAH-specific medications
- Vital status (including date/ cause of death)

The investigator can collect these data through direct contact with parent(s) / legally assigned representative or subjects as well as indirectly via the treating physician. Data can be collected via telephone call, site visit or through written communication (e.g., letter).

The investigator reports these data in the eCRF. Fatal events are additionally reported using an SAE form.

# 9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

## 9.1 Study Completion

For an individual subject study completion is reached when the EOS visit or the safety follow-up telephone call (if applicable) is completed.

The study is considered completed when the last subject completes the study (i.e., last EOS visit or last safety follow-up telephone call, whichever occurs last). The clinical database is locked after all data collected up to last subject last visit/contact have been collected and are considered accurate.

## 9.2 Premature Withdrawal from Study, Premature Study Visit Discontinuation

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 subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. 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 subject 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* or *change in/ discontinuation of SoC* (other than what is allowed according to protocol [see Sections 5.1.2 and 5.1.9] do not *per se* constitute premature withdrawal from the study. Every effort should be made to keep subjects in the study as per original schedule of assessments and hence allowing full data collection as per protocol until EOCP in order to reduce missing data. .

*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 EOCP. As a consequence, the subject enters the survival follow-up [refer to Section 8.17]. The date and reason for this premature study visit discontinuation will be reported in the eCRF. Efforts should be made so that the subject returns for a last site visit

before the survival follow-up starts (e.g., EOM for macitentan group, unscheduled visit for SoC group). The last survival follow-up contact will be used as the EOS.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual and/or respective parent(s) / legally designated representative failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document at least three ways of contact such as telephone number, home address, email address, person to be contacted in case the subject and/or parent(s) / legally designated representative cannot be reached). If the subject/parent(s) / legally designated representative cannot be reached, the site must make a reasonable effort to contact them, document all attempts, and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the parent(s) / legally designated representative or subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

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 subject, 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 subject is withdrawn from the study, the investigator should make efforts to schedule a last appointment/telephone call to assess the safety and wellbeing of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment/telephone call will be recorded in the subjects' medical records but it will not be collected in the eCRF. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

*Premature study discontinuation during Single-Arm Extension Period*: Premature discontinuation of macitentan during the SAEP or withdrawal from the SAEP will trigger an EOS visit. The same instruction provided for lost to follow-up and medical care after study withdrawal as described earlier will also apply during the SAEP.

## 9.3 Premature Termination or Suspension of the Study

The Sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is prematurely suspended or terminated, the investigators, the IECs/IRBs, and Health Authorities will be promptly informed as appropriate, and the reasons for the suspension or termination will be provided.

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with the Sponsor must promptly inform all enrolled subjects, and ensure their appropriate treatment and follow-up, as described in Section 9.2. The Sponsor (or delegate) may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates the study, the investigator must promptly inform the CRO personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

If the IEC/IRB suspends or terminates its approval/favorable opinion of the study, the investigator must promptly notify the CRO and provide a detailed written explanation of the termination or suspension.

The Sponsor must discuss any suspension or premature termination of the study with the IDMC.

## 9.4 Medical Care of Subjects After Study Completion/Withdrawal from Study

After the subject's study completion or premature withdrawal from study visits or from the study, whichever applies, the investigator/delegate will explain to subject's parent(s) / legally designated representative and to subjects who have come of age what treatment(s) / medical care is necessary and available according to local regulations. Such care may include:

- Continuation of SoC or of PAH background therapy.
- Recommendation to initiate any PAH-specific treatment, per investigator's judgment.
- Female subjects of childbearing potential and parent(s) / legally designated representative must be reminded that pregnancy must be prevented until EOS or until 30 days after last intake of macitentan and about acceptable methods of contraception if sexually active. Appropriate counseling regarding risks of pregnancy and reliable methods of contraception must be ensured.
- Participation to a PTA or LTE study for continuous macitentan access under a separate study protocol will be offered at EOS if available[refer to Section 3.1]. Subjects entering a Janssen PTA or LTE study will not have a Safety FU call in TOMORROW since their safety will be followed as part of the respective study.

# 10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

## 10.1 Adverse Events

### 10.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease with the exception of efficacy endpoints (i.e., PAH disease progression) and associated symptoms.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the signing of informed consent.
- Abnormal assessments, e.g., change in physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse, abuse and macitentan study treatment errors will be reported as an AE.

Overdose is defined as any dose that is higher than in described in Table 6 and Table 7 of Section 5.1.5. In adults macitentan has been administered as a single dose of up to 600 mg to healthy subjects. Adverse reactions of headache, nausea and vomiting were observed. In the event of overdose, standard supportive measures must be taken, as required. Due to the high degree of protein binding of macitentan, dialysis is unlikely to be effective. The investigator or treating physician should:

i. Immediately contact the Study Responsible Physician
ii. Evaluate the participant to determine, in consultation with the Study Responsible Physician, whether study intervention should be interrupted or whether the dose should be reduced

iii. Closely monitor the subject for AE/SAE and laboratory abnormalities for at least 14 days (by that time it is anticipated that the levels of macitentan and its active metabolite have returned to normal values)

iv. If requested by the Sponsor Medical Safety Physician (determined on a case-by-case basis) a plasma sample for PK analysis can be obtained within 3 days from the date of the last overdose of study intervention

v. Document the overdose as well as the duration of the overdosing in the eCRF.

Moreover, symptoms that are dependent on participant communication ability (e.g., nausea, pain, mood alterations) in younger or mentally disabled children could potentially be at risk for under- or mis-reporting. Study-site staff should instruct the legal guardians and caregivers on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc). These non-specific symptoms may be the only manifestations of some adverse reaction observed in infants and toddlers. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

### 10.1.2 Intensity of Adverse Events

The intensity of clinical AEs is graded on a three-point scale - mild, moderate, severe - and is reported on specific AE pages of the eCRF.

If the intensity of an AE worsens between randomization and EOS a new AE must be reported (including AEs ongoing at randomization). If the AE lessens in intensity, no change in the severity is required to be reported.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 10.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

### 10.1.3 Relationship to Study Treatment

For subjects in the macitentan group, each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to macitentan, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by the investigator.

### 10.1.4 Reporting of Adverse Events

All AEs with onset date after signing of informed consent and up to EOS or up to the safety follow-up telephone call (whichever is last) must be recorded on specific AE pages of the eCRF. Subjects who enter a PTA or LTE study at EOS will be waived from the safety follow-up call since they will be monitored in the respective PTA or LTE study. Exception: Events of exacerbation of underlying disease occurring until EOCP (see below).

Reporting of efficacy endpoint events:

- Core Period: All exacerbations of underlying disease during the Core Period must be reported on specific pages of the eCRF capturing disease progression where the information reported is similar to that captured for AEs (e.g., relationship to macitentan, action taken with macitentan). Such disease progression events and associated symptoms are not to be entered on the AE form of the eCRF.
- Single-Arm Extension Period: During the SAEP, all exacerbations of underlying disease will be reported on the AE form.

### 10.1.5 Follow-up of Adverse Events

AEs still ongoing after EOS or after safety follow-up telephone call (whichever is last) must be followed up until they are no longer considered clinically relevant (e.g., until symptom resolution) or until stabilization.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The follow-up information obtained after subjects' EOS / safety follow-up telephone call is recorded in the medical chart of the subject (source data), but is not recorded in the eCRF.

## 10.2 Serious Adverse Events

### 10.2.1 Definitions of Serious Adverse Events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Suspected transmission of any infectious agent via a medicinal product.
- Congenital anomaly or birth defect.
- Medically significant: Refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

### 10.2.2 Reporting of Serious Adverse Events

All SAEs, occurring after signing of informed consent and up to EOS or up to the safety follow-up telephone call (whichever is last) as well as product quality complaints (PQC) occurring during the study must be reported on AE pages in the eCRF (including the reason for seriousness) and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures. Subjects who enter a PTA or LTE study at EOS will be waived from the safety follow-up call since they will be monitored in the respective PTA or LTE study.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures (e.g., discontinuation of a subject's previous treatment during a washout period, leading to exacerbation of underlying disease).

PAH disease progression events that occur during the Core Period are recorded on dedicated eCRF pages ("Disease Progression Event Summary," "Disease Progression Event page," and if applicable "clinical worsening") but not in the AE section of the eCRF. However, serious events of PAH disease progression must be reported additionally using an SAE form. During the SAEP, disease progression events will be reported in the AE section of the eCRF and, if classified as "serious," on an SAE form.

### 10.2.3 Follow-up of Serious Adverse Events

SAEs still ongoing after the EOS visit or after the safety follow-up telephone call (whichever is last) must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the subject's EOS/ safety follow-up telephone call must be reported to the CRO, but it is not recorded in the eCRF.

During the SAEP, the investigator will report all SAEs directly to the Sponsor.

### 10.2.4 After the Study Period and Safety Follow-up Period

New SAEs occurring after EOS or after the safety follow-up telephone call (whichever is last) must be reported to the CRO within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

During the SAEP, the investigator will report these events directly to the Sponsor within 24 hours of their knowledge.

### 10.2.5 Reporting Procedures

All SAEs must be reported by the investigator to the CRO within 24 hours of the investigator's first knowledge of the event. The CRO will forward the SAE forms, blinded for treatment arm, to the Sponsor. During the SAEP, the SAEs will be directly reported to the Sponsor.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be sent to the CRO during the Core Period (contact details are provided on the SAE form), while they will be sent directly to the Sponsor during the SAEP. The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment for subjects in the macitentan group.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc, must be summarized on the SAE form.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The CRO personnel (or Sponsor personnel during the SAEP) may contact the investigator to obtain further information as instructed by the Sponsor.

If the subject is hospitalized in a hospital other than the study-site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

The expectedness of an adverse reaction is determined by the Sponsor in the reference safety information (RSI) section provided in the most recent version of the Investigator's Brochure. Any SAE that is assessed as related and unexpected against the RSI is known as a suspected unexpected serious adverse reaction and must be reported by the Sponsor to concerned Health Authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

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.

## 10.3 Pregnancy

If a female subject becomes pregnant while on study treatment with macitentan, study treatment must be discontinued [refer to Section 5.1.10]. The investigator must counsel the subject 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.

### 10.3.1 Reporting of Pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring in female participants or partners of male participants after study start (i.e., 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 applicable pregnancy notification form, which is sent to the CRO (see contact details provided on the respective Pregnancy form) during the Core Period, 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). Subjects who enter a PTA or LTE study at EOS will

be waived from the safety follow-up call since they will be monitored in the respective PTA or LTE study. The CRO will provide blinded pregnancy forms to the Sponsor. During the SAEP, the investigator will report the pregnancy directly to the Sponsor.

### 10.3.2 Follow-up of Pregnancy

Any pregnancy must be followed up to its conclusion and the outcome must be reported to the CRO on the applicable pregnancy notification form. During the SAEP, the pregnancy is reported directly to the Sponsor.

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 form as described in Section 10.2.5.

## 10.4 Study Safety Monitoring

Study safety information (AEs, SAEs, laboratory values, vital signs, Tanner stage and growth) is monitored and reviewed on a continuous basis by the responsible Clinical Team (in charge of ensuring subjects' safety as well as data quality). In addition, an IDMC is monitoring safety data [see Section 3.4].

## 10.5 Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

### 10.5.1 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.

### 10.5.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

## 10.6 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, e.g., 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.

# 11 STATISTICAL METHODS

All statistical analyses will be conducted by a designated CRO supervised by the Sponsor. The firewalls put in place between blinded and unblinded study team members are described in a dedicated Firewall Charter.

A SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

## 11.1 Analysis Sets

### 11.1.1 Screened Analysis Set

The Screened Analysis Set includes all subjects who were screened and have a subject identification number.

### 11.1.2 Full Analysis Set

The Full Analysis Set 1 (FAS1) includes all subjects assigned to a study treatment via IRT (all randomized subjects ≥ 2 y.o. at randomization).

In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the study treatment they have been assigned to via IRT (which may be different from the study treatment they have actually received),
- All available data are taken into account.

FAS2 includes all subjects less than 2 y.o. at Visit 2 who are assigned to macitentan without randomization.

FAS3 includes all subjects (subjects ≥ 2 y.o.) assigned to a study treatment via IRT (FAS1) and all subjects less than 2 y.o. assigned to macitentan without randomization (FAS2).

### 11.1.3 Safety Set

The Safety Set includes all subjects who received at least one dose of macitentan or who were randomized to continue the planned SoC. Subjects will be analyzed based on actual treatment received pre-event SP (which may be different to the study treatment arm they have been randomized to).

Subjects < 2 y.o. at Visit 2 will be summarized separately.

### 11.1.4 Pharmacokinetic Analysis Sets

The PK Set 1 includes all subjects randomized to and treated with macitentan, for whom a PK blood sample at trough has been taken and who do not deviate from the protocol in a way that might affect the evaluation of the PK trough endpoints.

The PK Set 2 includes all subjects ≥ 2 y.o. randomized to and treated with macitentan or crossing over to macitentan and part of the PK substudy, who have evaluable PK profiles and who do not deviate from the protocol in a way that might affect the evaluation of the PK substudy endpoints.

The PK Set 3 includes all subjects < 2 y.o. treated with macitentan, for whom a PK blood sample has been taken and who do not deviate from the protocol in a way that might affect the evaluation of the PK endpoints.

### 11.1.5 Usage of the Analysis Sets

The FAS1 is used for the main analyses of all the secondary efficacy and exploratory variables.

The FAS2 is used for descriptive analyses of all secondary efficacy and exploratory variables.

The FAS3 is used for the description of the study population at Baseline. Unless specified otherwise, individual listings are prepared on the FAS3.

The Safety Set is used for the analyses of the safety variables.

The Screened Analysis Set is used for the description of subject disposition.

For macitentan and ACT-132577 trough concentration analysis, the PK Set 1 (≥ 2 y.o.) and PK Set 3 (< 2 y.o.) will be used. For PK substudy analysis, the PK Set 2 (≥ 2 y.o.) and PK Set 3 will be used.

## 11.2 Variables

All variables described thereafter are related to the endpoints defined in Section 6.

### 11.2.1 Primary Variable

In subjects who are ≥ 2 y.o.: in the macitentan arm:

- Trough plasma concentrations of macitentan and its active metabolite ACT-132577 at Week 12 (steady-state conditions)

In subjects < 2 y.o.:

- Trough concentrations of macitentan and ACT-132577 at Week 4 (steady-state conditions)

PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight (≥ 2 y.o.) and age (< 2 y.o.) groups.

### 11.2.2 Secondary efficacy variables

Secondary efficacy variables described here below are related to the secondary efficacy endpoints described in Section 6.1.2.

#### 11.2.2.1 *Time to First CEC-confirmed Disease Progression*

All disease progressions occurring from randomization (or Visit 2 for subjects < 2 y.o.) until EOCP are considered, irrespective of subjects compliance to assigned therapies.

Subjects who do not experience any CEC-confirmed disease progression before the end of the Core Period have their time to first disease progression right-censored at the time of EOCP visit or cutoff date for the respective analysis, whichever occurs first. For subjects who discontinue prematurely regular study visits the last survival follow-up contact will be used as the EOCP visit. Time to first disease progression is expressed in days and calculated as the onset date of the first CEC-confirmed disease progression minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1 or, for censored subjects, as censoring date minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1.

The events to be considered for the first CEC-confirmed disease progression are described in Section 6.1.1.

#### 11.2.2.2 *Time to First CEC-confirmed Hospitalization for PAH*

All hospitalizations occurring from randomization (or Visit 2 for subjects < 2 y.o.) until EOCP are considered, irrespective of subjects' compliance to assigned therapies.

Subjects who do not experience any CEC-confirmed hospitalization for PAH before the end of the Core Period, have their time to first hospitalization right-censored at the time of EOCP visit or cutoff date for the respective analysis, whichever occurs first. Subjects who discontinue prematurely regular study visits are censored at the time of the last study visit performed (end of adjudication).

Time to first hospitalization is expressed in days and calculated as the onset date of the first CEC-confirmed hospitalization minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1 or, for censored subjects, as censoring date minus date of randomization (or enrolment for subjects < 2 y.o.) plus 1.

#### 11.2.2.3 *Time to CEC-confirmed Death Due to PAH*

All deaths occurring from randomization (or Visit 2 for subjects < 2 y.o.) until EOCP are considered, irrespective of subjects' compliance to assigned therapies.

Subjects who have not died due to PAH before study completion have their time to death right-censored at the time of EOCP visit or cutoff date for the respective analysis, whichever occurs first. Subjects who discontinue prematurely regular study visits are censored at the time of the last study visit performed (end of adjudication).

Time to death is expressed in days and calculated as the onset date of the CEC-confirmed death for PAH minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1 or, for censored subjects, as censoring date minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1.

#### 11.2.2.4 *Time to Death (All Causes)*

All deaths occurring from randomization (or Visit 2 for subjects < 2 y.o.) until EOS are considered, irrespective of subjects' compliance to assigned therapies.

Subjects still alive at study closure have their time to death right-censored at the time of EOS or cutoff date for the respective analysis , whichever occurs first. For subjects who discontinue prematurely regular study visits, the last survival follow-up contact will be used as the EOS.

Time to death is expressed in days and calculated as the date of death minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1 or, for censored subjects, as censoring date minus date of randomization (or Visit 2 for subjects < 2 y.o.) plus 1.

#### 11.2.2.5 *WHO FC I or II (Yes/no) at Week 24*

It is the WHO FC value categorized as I/II versus III/IV at 24 weeks. The WHO FC value will also be categorized at every timepoint of assessment. The proportion of subjects with WHO FC equal to I or II is described for every timepoint of assessment based on the number of subjects with available data (i.e., those having a reported value of I through IV) and only considering values collected up to end of randomized macitentan or SoC + 7 days.

For subjects < 2 y.o. who enter macitentan arm without randomization values collected until end of macitentan study treatment + 7 days are considered.

#### 11.2.2.6 *Percent of Baseline in Plasma NT-proBNP at Week 24*

It is the percent of Baseline at 24 weeks in plasma NT pro-BNP, defined as:

$$\left[\frac{NT\ pro-BNP\ at\ time\ point}{NT\ pro-BNP\ at\ Baseline}\right]\times 100$$

The percent of baseline in plasma NT pro-BNP will also be calculated at every timepoint of assessment and only considering values collected up to end of randomized macitentan or SoC + 7 days.

For subjects < 2 y.o. who enter macitentan arm without randomization values collected until end of macitentan study treatment + 7 days are considered.

#### 11.2.2.7 *Mean Daily Time Spent in Moderate to Vigorous Physical Activity as Measured by Accelerometry at Week 48*

It is the change from baseline to Week 48 in mean daily time spent in moderate to vigorous physical activity as measured by accelerometry.

The change from baseline to Weeks 12 and 24 will also be presented. All accelerometry variables will only consider values collected up to end of randomized macitentan or SOC + 7 days.

These additional variables will be expressed as change from Baseline as well. All accelerometry variables will also be presented as change from Baseline to Week 12 and 24 and only considering values collected up to end of randomized macitentan or SoC + 7 days.

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].

#### 11.2.2.8 *Echocardiography Variables at Week 24*

The echocardiographic variables of interest are TAPSE and left ventricular eccentricity index expressed as change from Baseline to Week 24. The echocardiographic variables will also be expressed as change from Baseline to Week 12 and only considering values collected up to end of randomized macitentan or SoC + 7 days.

For subjects < 2 y.o. who enter macitentan arm without randomization values collected until end of macitentan study treatment + 7 days are considered.

#### 11.2.2.9 *Quality of Life As Measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15) At Week 24*

Expressed as change from Baseline to 24 weeks. The change from Baseline to each post-Baseline timepoint of assessment will also be presented and only considering values collected up to end of randomized macitentan or SoC + 7 days.

The quality of life variables are further defined in Section 11.2.5.

### 11.2.3 Exploratory Variables

This section contains definitions of the variables related to the exploratory endpoints outlined in Section 6.1.3.

#### 11.2.3.1 *Panama FC I or II (yes/no) at Week 24*

It is the Panama FC value categorized as I/II versus III/IV at Week 24. The Panama FC values is also categorized at every timepoint. The proportion of subjects with Panama FC equal to I or II is described for every timepoint of assessment based on the number of subjects with available data (i.e., those having a reported value of I through IV) and only considering values collected up to end of randomized macitentan or SoC + 7 days.

For subjects < 2 y.o. who enter macitentan arm without randomization values collected until end of macitentan study treatment + 7 days are considered.

#### 11.2.3.2 *Additional Physical Activity (Accelerometry) at Weeks 12, 24 and 48*

The additional 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.

Expressed as change from Baseline to Weeks 12, 24, and 48 and only considering values collected up to end of randomized macitentan or SoC + 7 days.

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].

#### 11.2.3.3 *Six-minute Walk Distance at all Time Points*

The variable of interest is 6-minute walk distance expressed as change from Baseline to all timepoints, and only considering values collected up to end of randomized macitentan or SoC + 7 days.

### 11.2.4 Safety Variables

Safety variables described here below are related to the safety endpoints described in Section 6.2.

The safety variables are the following:

- AEs from randomization up to EOS
  AEs leading to premature discontinuation of randomized macitentan or SoC
  AEs with fatal outcome
  AEs of special interest (as defined in the SAP)
- Treatment-emergent AEs up to end of randomized macitentan or SoC + 30 days
- SAEs up to EOS
- Marked laboratory abnormalities up to EOS
- Change from Baseline in selected laboratory variables [refer to Section 11.3.5.2] to all timepoints of assessments up to EOS
- Change from Baseline in vital signs (BP, heart rate) to all timepoints up to EOS
- Growth from Baseline to all timepoints of assessments up to end of randomized macitentan or SoC + 30 days
- Sexual maturation (Tanner stage) change from Baseline to all timepoints of assessments up to end of randomized macitentan or SoC + 30 days

Baseline is the last non-missing value observed before or on the day of randomization.

For subjects < 2 y.o. who enter macitentan arm without randomization the day of randomization equals the day of Visit 2 and end of randomized macitentan refers to end of macitentan study treatment.

Treatment emergent AEs are defined as any AEs occurring after randomization up to end of randomized macitentan or SoC + 30 days.

### 11.2.5 Quality of Life at Each Timepoint of Assessment

The Pediatric Quality of Life Inventory™ (PedsQL™) questionnaire is used and the QoL variables of interest are:

- PedsQL™ 3.0 Cardiac Module score (English-speaking US subjects)
- PedsQL™ Multidimensional Fatigue Scale score (English-speaking US subjects)

Expressed as change from Baseline to each post-Baseline timepoint of assessment and only considering values collected up to end of randomized macitentan or SoC + 7 days. The mean score for each scale is calculated according to the algorithm in the scoring manual [Peds QL™ 2014]. Where applicable the total score is used in calculation of the mean.

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

### 11.2.6 Pharmacokinetic Variables

In a subpopulation of subjects ≥ 2 y.o. receiving macitentan treatment as randomized or after crossover (up to 40 subjects distributed over the different age groups) for both macitentan and ACT-132577 at steady-state conditions:

- PK profile over 24 hours at pre-dose and following administration of macitentan during steady-state conditions
- $AUC_{\tau}$
- $C_{max}$ during a dosing interval
- $t_{max}$ during a dosing interval

In subjects younger than 2 y.o.:

- Concentrations after the first dose of macitentan within 24 hours (2, 5, 24h post-dose) and trough concentrations at steady state
- Concentrations will be summarized descriptively per timepoint.

### 11.2.7 Palatability and Acceptability of Macitentan

Palatability and acceptability of macitentan dispersible formulation on Day 1 and at Week 12 are assessed on 5-point facial hedonics (refer to Appendix 6).

## 11.3 Description of Statistical Analyses

### 11.3.1 Analysis of the Primary Variable

For PK trough analysis in all subjects, the PK Set 1 will be used.

PK data will be listed by subject number, and PK endpoints will be analyzed descriptively by body weight group for those who are 2 years or older or by age group for those who are < 2 y.o.

Plasma and blood concentrations of macitentan and ACT-132577 per timepoint will be summarized by body weight or age group in ≥ 2 y.o. and < 2 y.o., respectively, using arithmetic mean and geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and 2-sided 95% CI of the mean.

Subgroup analyses will be described in the SAP.

### 11.3.2 Analysis of the Time to Event Secondary Efficacy Variables

The analysis of the time to event variables will be performed on subjects of the FAS1 (subjects ≥ 2 y.o.), according to the intent-to-treat principle.

At Analysis 1 cutoff date, treatment effect estimates and 95% CLs will be provided for exploratory purposes only. No multiplicity adjustment will be applied. Analysis 2 cutoff date will be the primary analyses for these endpoints; p-values will be provided in addition to the treatment effect estimates and 95% CLs. Further details will be described in the SAP.

The analysis of the time to event variables will only be descriptive for subjects of the FAS2 (less than 2 y.o. receiving macitentan) at Analysis 1 and 2 cutoff dates.

#### 11.3.2.1 *Main Analysis*

The main analysis of the time to event efficacy variables will be carried out using a 2-sided stratified log-rank test with stratification factors: ongoing/planned ERA treatment (yes vs no) and WHO FC (FC I/II vs FC III) at randomization as documented in the IRT. The resulting 2-sided p-value will be provided.

The treatment effect will be estimated based on a proportional hazards Cox model adjusting for the same stratification factors. Estimates of each HR and its associated 95% CL will be displayed.

Kaplan-Meier estimates will be calculated with 2-sided 95% CLs at relevant time-points for each treatment group and displayed in both a graphical (where the number of subjects at risk is at least 10% of the total number of subjects in the analysis set) and a tabular form. In addition, the number of subjects at risk, the number of subjects censored and the number of subjects with event will be computed at each timepoint and for each treatment group.

#### 11.3.2.2 *Supportive/sensitivity Analyses*

#### 11.3.2.3 *Supportive/sensitivity analyses will be described in the SAP. Subgroup Analyses*

In order to assess the consistency of the treatment effect across different subject subgroups for the time to event secondary efficacy variables, subgroup analyses are performed according to the demographic and Baseline disease characteristics at randomization:

- WHO FC (FC I/II vs FC III),

- Ongoing/planned ERA treatment at randomization (yes vs no),
- Ongoing/planned PDE-5i treatment at randomization (yes vs no),
- PAH etiology ([iPAH, hPAH, HIV, drug or toxin induced]vs [PAH with co-incidental CHD, CHD post-operative] vs [PAH-aCTD]),
- Geographical region (North America vs Europe/Israel vs Asia/Australia vs Other),
- Age (≥ 2 to < 6 years / ≥ 6 to < 12 years / ≥ 12 to < 18 years),
- Sex (male vs female).

Subgroup analyses will be described in the SAP.

Further subgroups will be added for analysis if deemed appropriate.

#### 11.3.2.4 *Handling of Missing Data*

Due to the nature of the time to event secondary efficacy variables, subjects with no CEC-confirmed disease progression have their time to disease progression right-censored at the time of EOCP, or cutoff date for the respective analysis , whichever comes first. No additional imputation method will be used.

The nature of the censoring process will be investigated by plotting the survival distribution of the time to censoring (where censored data for main analysis event, and event for main analysis censored data) for both treatment groups using the Kaplan-Meier product-limit method.

The following table illustrates different possible cases and the outcome for time to CEC-disease progression analysis:

| **Compliance to study Follow-up** | **Situation*** | **Date of disease progression or Censoring** | **Outcome** |
|---|---|---|---|
| Subject completes regular study visits up to EOCP | Disease progression or death documented during a regular study visit up to EOS | Date of first documented disease progression or death | Event |
| | No disease progression up to EOS | Earliest between EOS date and cutoff date for the respective analysis | Censored<br>*Reason:* Study completed |
| Subject prematurely discontinues regular study visits AND completes survival follow-up until EOCP | Disease progression documented during a regular study visit | Date of first documented disease progression | Event |
| | No disease progression during regular study visits<br>AND death | Date of death | Event |
| | No disease progression during regular study visits<br>AND no death | Earliest between last survival follow-up contact date and cutoff date for the respective analysis | Censored<br>*Reason:* Study completed |
| Subject prematurely discontinues regular study visits and/or survival follow-up before EOCP | Disease progression documented during a regular study visit | Date of first documented disease progression | Event |
| | No disease progression during regular study visits AND death | Date of death | Event |
| | No disease progression during regular study visits<br>AND no death | Earliest between last regular study visit and last survival follow-up contact date | Censored<br>*Reason:* as reported on 'End of study' eCRF page |

* All disease progressions have to be CEC confirmed

CEC Clinical Event Committee; eCRF electronic case report form; EOCP end of core period; EOS end of study.

Missing data handling and the censoring rules for the other time to event variables will be described in the SAP.

### 11.3.3 Other Secondary Efficacy Variables

The analysis of other secondary efficacy variables will be carried out on the FAS1 (subjects ≥ 2 y.o.) and will only consider values collected up to end of randomized macitentan or SoC + 7 days.

At Analysis 1 cutoff date, treatment effect estimates and 95% CLs will be provided for exploratory purposes only. Analysis 2 cutoff date will be the primary analyses for these endpoints; p-values will be provided in addition to the treatment effect estimates and 95% CLs.

The analysis of the other secondary efficacy variables will only be descriptive for subjects of the FAS2 (less than 2 y.o. receiving macitentan) at Analysis 1 and 2 cutoff dates.

#### 11.3.3.1 *Percent of Baseline in Plasma NT-proBNP at Week 24*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

The percent of Baseline at each timepoint of assessment will be evaluated with the use of a repeated measures mixed model on the log-transformed NT-proBNP values (including Baseline). The model will include randomized treatment, visit, treatment by visit interaction, the 2 randomization stratification factors as fixed effects and log transformed Baseline NT-proBNP as a fixed covariate, while subject will be included as a random effect. Each timepoint of assessment will be assessed with the comparison at Week 24 being the most relevant.

The treatment effect expressed as geometric means ratio and its associated 95% 2-sided CIs will be then estimated at each post-Baseline timepoint of assessment by inversely transforming, using the exponential function, the difference in change from Baseline between treatment groups and the associated 95% CIs, both estimated via the above model in log scale.

Adjusted geometric means within each treatment group and ratios of adjusted geometric means of percent of baseline between treatment groups will be displayed for each visit along with their corresponding 2-sided 95% CIs and p-values.

If the treatment by visit interaction is not significant at the 0.01 level then the model will be re-run without the interaction term and the overall averaged treatment effect will be presented with 2-sided 95% CI and p-value.

Plot of NT-proBNP profile over time will be provided considering observed NT-proBNP values (original scale).

#### 11.3.3.2 *WHO FC I or II (Yes/no) at Week 24*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

The proportion of subjects having WHO FC I or II will be calculated at each timepoint of assessment, and compared between the two treatment groups by means of a stratified logistic regression. The two stratification factors will be ongoing/planned ERA treatment (yes vs no) and WHO FC (FC I/II vs FC III) at randomization as documented in the IRT. The odds ratio (macitentan/SoC) will be displayed with 2-sided 95% CLs. Each timepoint of assessment will be assessed with the comparison at Week 24 being the most relevant.

In addition to the stratified analysis, an unstratified logistic regression will be performed.

Plot of WHO FC profile over time will be provided.

#### 11.3.3.3 *Mean Daily Time Spent in Moderate to Vigorous Physical Activity as Measured by Accelerometry at Week 48*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

Changes from Baseline in mean daily time spent in moderate to vigorous physical activity as measure by accelerometry defined in Section 11.2.2.7 will be analyzed over time by means of a repeated measures mixed model on values at each visit (including Baseline). The model will include randomized treatment, visit, treatment by visit interaction, the 2 randomization stratification factors as fixed effects and the baseline value as fixed covariate, while subject will be included as a random effect. Each timepoint of assessment will be assessed with the comparison at Week 24 being the most relevant.

Adjusted least squares means within each treatment group and adjusted estimates of the differences in change from Baseline between treatment groups will be displayed for each visit along with their corresponding 2-sided 95% CIs and p-values.

If the treatment by visit interaction is not significant at the 0.01 level then the model will be re-run without the interaction term and the overall averaged treatment effect will be presented with 2-sided 95% CI and p-value.

Plots of physical activity profiles over time will be provided.

#### 11.3.3.4 *Echocardiography Variables at Week24*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

The change from Baseline to Weeks 12 and 24 in echocardiography variables defined in Section 11.2.2.8 will be described over time by means of repeated measures mixed models as described for physical activity variables in Section 11.3.4.2. Each timepoint of assessment will be assessed with the comparison at Week 24 being the most relevant.

Plots of echocardiography variables profiles over time will be provided.

#### 11.3.3.5 *Quality of Life As Measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15) at Week 24*

The analysis of QoL variables as measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15) are described in the QoL Section 11.3.6. Each timepoint of assessment will be assessed with the comparison at Week 24 being the most relevant.

### 11.3.4 Analysis of the Exploratory Variables

The analysis of exploratory variables will be carried out on the FAS1 (subjects ≥ 2 y.o.) and will only consider values collected up to end of randomized macitentan or SoC + 7 days.

Due to the nature of these analyses, at Analysis 1 cutoff date, treatment effect estimates and 95% CLs will be provided for exploratory purposes only. At Analysis 2 cutoff date, two-sided p-values will be provided in addition to the treatment effect estimates and 95% CLs for exploratory purposes only.

The analysis of these efficacy variables will only be descriptive for subjects of the FAS2 (< 2 y.o. receiving macitentan) at Analysis 1 and 2 cutoff dates.

#### 11.3.4.1 *Panama FC I or II (Yes/no) at Week 24*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

The proportion of subjects will be analyzed at each timepoint of assessment using the same methods outlined in Section 11.3.3.2 for the WHO FC endpoint.

Plot of Panama FC profile over time will be provided.

#### 11.3.4.2 *Other Physical activity variables (accelerometry) at Weeks 12, 24 and 48*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

Changes from Baseline in accelerometry variables defined in Section 11.2.3.2will be analyzed over time by means of a repeated measures mixed model on values at each visit. The model will include randomized treatment, visit, treatment by visit interaction, the 2

randomization stratification factors and baseline value as fixed effects, while subject will be included as a random effect.

Adjusted least squares means within each treatment group and adjusted estimates of the differences in Change from Baseline between treatment groups will be displayed for each visit along with their corresponding 2-sided 95% CIs and p-values.

If the treatment by visit interaction is not significant at the 0.01 level then the model will be re-run without the interaction term and the overall averaged treatment effect will be presented with 2-sided 95% CI and p-value.

Plots of physical activity profiles over time will be provided.

#### 11.3.4.3 *Six-minute Walk Distance at Weeks 12, 24 and 48*

Only values collected up to end of randomized macitentan or SoC + 7 days will be considered for this analysis.

The change from Baseline to Weeks 12, 24 and 48 in 6-minute walk distance will be described over time by means of repeated measures mixed models as described for physical activity variables in Section 11.3.3.3.

Plots of 6-minute walk distance profile over time will be provided.

### 11.3.5 Analysis of the Safety Variables

Analysis of the safety variables will be from randomization (or Visit 2 for subjects less than 2 y.o.) until EOS. AEs will be summarized during the Core Period and open label extension period. The time periods of interest for the analyses of the safety variables will be defined in the SAP.

#### 11.3.5.1 *Adverse Events*

All AEs are coded with MedDRA and will be analyzed on the Safety Set by treatment arm.

The number and percentage of subjects with at least one AE, number and percentage of subjects with at least one SAE, number and percentage of subjects with at least one AE leading to premature discontinuation of randomized macitentan or SoC, and number and percentage of subjects with at least one AE with fatal outcome up to EOS will be tabulated by randomized treatment group and by:

- System organ class and individual preferred term within each system organ class, in descending order of incidence within the macitentan treatment group,
- Preferred term, in descending order of incidence in the macitentan treatment group.

Furthermore, for subjects exposed to macitentan, the number and percentage of subjects with at least one AE according to intensity, number and percentage of subjects with at least

one AE according to relationship to macitentan, and number and percentage of subjects with at least one SAE according to relationship to macitentan up to EOT + 30 days will be tabulated by:

- System organ class and individual preferred term within each system organ class, in descending order of incidence within macitentan treatment group,
- Preferred term, in descending order of incidence in the macitentan treatment group.

The worst intensity among 'mild' 'moderate and 'severe' during the studied period will be considered if the same AE is reported more than once for the same subject. AEs with missing intensity will be counted as 'severe.'

The worst relationship among 'not related' and '**related**' during the studied period will be considered if the same AE is reported more than once for the same subject. AEs with missing relationship will be counted as 'related.'

**For subjects randomized to the SoC arm and who received macitentan after CEC-confirmed disease progression,** the number and percentage of subjects with at least one AE; number and percentage of subjects with at least one SAE; number and percentage of subjects with at least one AE leading to premature discontinuation of macitentan (initiated at cross-over); number and percentage of subjects with at least one AE with fatal outcome; number and percentage of subjects with at least one AE according to intensity; number and percentage of subjects with at least one AE according to relationship to macitentan; and number and percentage of subjects with at least one SAE according to relationship to macitentan will be tabulated by:

- System organ class and individual preferred term within each system organ class, in descending order of incidence within the macitentan treatment group,
- Preferred term, in descending order of incidence in the macitentan treatment group

**For adverse events of special interest**, the following analyses will be performed:

- Number and percentage of subjects with at least one AE of special interest by treatment group and preferred term in the overall Safety set population as well as by age categories (≥ 2 to < 6 years / ≥ 6 to < 12 years / ≥ 12 to < 18 years) and sex (female vs male).
- Kaplan-Meier estimates of the time to first of each AESI will be calculated with 2-sided 95% CIs at relevant timepoints for each treatment group and displayed in both a graphical form (where the number of subjects at risk is at least 10% of the total number of subjects in the analysis set) and a tabular form. In addition, the number of subjects at risk, the number of subjects censored and the number of subjects with event will be computed at each timepoint and for each treatment group.

**For subjects enrolled in the single-arm extension period,** the number and percentage of subjects with at least one AE; number and percentage of subjects with at least one SAE; number and percentage of subjects with at least one AE leading to premature discontinuation of macitentan (during the SAEP); number and percentage of subjects with at least one AE with fatal outcome; number and percentage of subjects with at least one AE according to intensity; number and percentage of subjects with at least one AE according to relationship to macitentan; and number and percentage of subjects with at least one SAE according to relationship to macitentan will be tabulated by treatment group and by:

- System organ class and individual preferred term within each system organ class, in descending order of incidence within the macitentan treatment group,
- Preferred term, in descending order of incidence in the macitentan treatment group.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for all AEs leading to premature discontinuation of randomized macitentan treatment, for all AEs leading to death, for all AEs occurring in the SoC arm after cross-over to macitentan, for all AEs occurring in the SAEP and for all AEs leading to premature discontinuation of macitentan at any time.

#### 11.3.5.2 *Laboratory Variables*

All Central Laboratory data transferred to the clinical database will be taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments. All recorded assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment using the usual location and scale summary statistics by treatment group.

Treatment-emergent marked laboratory abnormalities will be analyzed on the Safety Set by treatment arm.

A dictionary listing of definitions of marked laboratory abnormality (LL, LLL, HH, HHH) will be provided for each variable.

For each category (i.e., LL, LLL, HH, HHH, HHHH), treatment-emergent marked laboratory abnormalities are summarized for each laboratory variable by treatment group displaying counts and percentages of subjects with at least a treatment-emergent marked laboratory abnormality. Percentages are calculated as number of subjects with at least once the abnormality for the variable under consideration divided by the number of subjects with any post-Baseline laboratory measurement (and for hemoglobin and creatinine, also with a valid Baseline value based on the definition of the abnormality).

Specifically for erythrocytes, hemoglobin, hematocrit, AST, ALT, total bilirubin, and alkaline phosphatase, the following analyses will be performed:

- Absolute values and changes from Baseline will be summarized over time up to EOS.
- Plots of profiles over time will also be provided.
- Kaplan-Meier estimates of the time to first marked abnormalities will be calculated with 2-sided 95% CIs at relevant timepoints for each treatment group and displayed in both a graphical form (where the number of subjects at risk is at least 10% of the total number of subjects in the analysis set) and a tabular form. In addition, the number of subjects at risk, the number of subjects censored and the number of subjects with event will be computed at each timepoint and for each treatment group.

In addition, scatter plots of the worst post-Baseline value (vertical axis) versus Baseline value (horizontal axis) will be displayed for each laboratory variable, once transformed as follows:

*Transformed value (Worst post-Baseline value LLN) / (ULN LLN)*

Vertical and horizontal lines representing the transformed references ranges (0 for lower limit and 1 for upper limit) will be added to the plot. For laboratory variables that could worsen toward either low or high value, two separate plots will be performed, one for each worsening direction.

Finally, the emergence of potential Hy's Law cases will be explored by providing, for each of the following conditions, the number and frequency of subjects meeting the condition for at least one post-Baseline visit, provided the condition was not already present at Baseline:

- ALT > 3 × ULN at any time,
- ALT and/or AST > 3 × ULN at any time,
- ALT > 5 × ULN at any time,
- ALT and/or AST > 5 × ULN at any time,
- ALT > 8 × ULN at any time,
- ALT and/or AST > 8 × ULN at any time,
- ALT and/or AST > 3 × ULN + total bilirubin (TBIL) > 2 × ULN at any time,
- ALT or AST > 3 × ULN + TBIL > 2 × ULN at the same time,
- ALT or AST > 3 × ULN + TBIL > 2 × ULN + AP < 2 × ULN at the same time,
- TBIL > 2 × ULN at any time.

eDISH plots will also be provided to facilitate exploration [Watkins 2011].

**For subjects who received macitentan after CEC-confirmed disease progression,** all the above analyses will be reproduced.

**For subjects who enroll in the single-arm extension period**, all the above analyses will be reproduced.

All available local laboratory data will be listed by subject.

#### 11.3.5.3 *Vital Signs*

BP (i.e., diastolic BP and systolic BP) and heart rate will be described over time by means of repeated measures mixed models as described for physical activity variables in Section 11.3.4.2. Mixed models will be used to handle missing data under missing at random (MAR) assumption.

Plots of vital signs profiles over time will be provided.

#### 11.3.5.4 *Growth*

Growth variables body mass index, height and weight, will be analyzed over time by means of repeated measures mixed models as described for physical activity variables in Section 11.3.4.2. Mixed models will be used to handle missing data under MAR assumption.

In addition, body weight (kg) and body length/height (cm) will be plotted over time as individual curves per subject. The x-axis will display age in months. The y-axis will display the growth variable of interest, weight (kg) or length/height (cm). Separate figures will be created for male and female subjects with/without Down Syndrome, with overlays of sex-specific standard WHO growth percentiles by age for the $5^{th}$, $25^{th}$, $50^{th}$, $75^{th}$, and $95^{th}$ percentiles. All collected values of weight and length/height will be used.

A different symbol will be used for each treatment group.

#### 11.3.5.5 *Sexual Maturation (Tanner Stage)*

Sexual maturation changes from baseline as measured by the Tanner stage will be summarized at each scheduled time point by intervention group.

In addition, summary tables will be provided by treatment group for childbearing potential at each timepoint of assessment.

### 11.3.6 Quality of Life

The analysis of QoL variables will be carried out on the FAS1 and will only consider values collected up to end of randomized macitentan or SoC + 7 days.

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

Changes from Baseline in QoL scores defined in Section 11.2.5 will be analyzed over time by means of a repeated measures mixed model on values at each visit . The model will include randomized treatment, visit, treatment by visit interaction, the 2 randomization

stratification factors as fixed effect and Baseline value as fixed covariate, while subject will be included as a random effect.

Adjusted least squares means within each treatment group and adjusted estimates of the differences in change from Baseline between treatment groups will be displayed for each visit along with their corresponding 2-sided 95% CIs and p-values.

If the treatment by visit interaction is not significant at the 0.01 level then the model will be re-run without the interaction term and the overall averaged treatment effect will be presented with 2-sided 95% CI and p-value.

Plots of QoL variables profiles over time will be provided.

Spider plots displaying for every problem, the percentage of subjects with the problem will also be generated at Week 12, Week 24, Week 48 and Week 96.

### 11.3.7 Analysis of pharmacokinetic variable(s)

For PK profiles in children > 2 y.o., the PK Set 2 will be used, and PK Set 3 will be used for PK assessment in children < 2 y.o

PK data will be listed by subject number and PK endpoints will be analyzed descriptively by body weight (≥ 2 y.o.) and age (< 2 y.o.) groups.

Plasma or blood concentrations of macitentan and ACT-132577 per timepoint will be summarized by body weight group or age group, respectively, using arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and 2-sided 95% CI of the mean.

Maximum plasma or blood concentration ($C_{max}$), the area under the plasma/ blood concentration-time curve during one dosing interval ($AUC_{\tau}$) and the time to reach maximum plasma/ blood concentration ($t_{max}$)* will be summarized with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, coefficient of variation inter-subject in %, and 95% CI of the arithmetic and geometric means.

* For $t_{max}$ the geometric mean and its 95% CI will not be calculated.

Population pharmacokinetic analysis maybe undertaken as deemed appropriate. If undertaken, the analysis details will be described separately.

The following assumptions have been made:

- $C_{max}$, AUC, and $t_{½}$ values are assumed to be log-normally distributed [Julious 2000].
- No period or carry-over effects.

The measured individual concentrations of macitentan and ACT-132577 will be used to directly obtain $C_{max}$ and $t_{max}$.

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

### 11.3.8 Palatability and Acceptability

Palatability and acceptability of macitentan dispersible formulation on Day 1 and at Week 12 assessed on a hedonic facial scale, will be summarized separately with counts and percentages using the safety analysis set.

## 11.4 Interim Analysis

Interim analyses are planned to allow assessment of emerging PK, efficacy and safety data and support regulatory interactions. Three analysis time points are considered (Section 3.1).

There will be three time points of study analysis:

- Analysis 1 (interim analysis for Core Period): with cutoff date in the fourth quarter of 2022
- Analysis 2 (final analysis for Core Period): with cutoff date in the first quarter of 2024
- Analysis 3 (final analyses including the core and the single-arm extension periods):

## 11.5 Sample Size

The sample size of approximately 200 subjects and not more than 300 subjects is driven by feasibility and no formal sample size calculations are provided. The study recruitment will be closed by fourth quarter of 2023 to allow at least 12 weeks study follow-up for Analysis 2 in first quarter of 2024. Analysis 1 and 2 cutoff dates are driven by the regulatory timelines.

# 12 DATA HANDLING

## 12.1 Data Collection

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

Electronic Case Report Form (eCRF) data will be captured via electronic data capture ( using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification - an

electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).Subject screening and enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject screened, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject is withdrawn from the study, the reason must be noted on the eCRF. For screening failures the eCRF is only completed for Baseline assessments collected before confirmation of non-eligibility of the subject.

A third party (CRO) will carry out the data management. The Sponsor will work with the CRO following a detailed oversight plan which will ensure that oversight of quality is maintained.

## 12.2 Maintenance of Data Confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to the Sponsor, the CRO and any other external service providers, subjects must be identified only by number, and never by their name or initials, hospital numbers, or any other identifier. The investigator/delegate must keep a subject identification code list, at the site, showing the screening/randomization number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICF) must not be sent to the CRO nor to the Sponsor, and must be kept in strict confidence by the investigator/delegate.

## 12.3 Database Management and Quality Control

The investigators will have access to the site eCRF data until the database is closed. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any timepoint during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review (including medical review) will be performed by the sponsor/CRO personnel on an ongoing basis to look for discrepancies or unexpected patterns in data and for study monitoring. If discrepant data are detected or clarification is required, a query specifying the problem or question will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. This process will continue until database closure.

The investigator/delegate must, on request, supply the CRO with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

For data processed by central readers/laboratories (e.g., Laboratory) the results will be sent electronically to the CRO.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate Standard Operating Procedure (SOP). After database closure, the investigator will receive the eCRFs of the subjects of his/her site (including all data changes made) on electronic media or as a paper copy.

# 13 PROCEDURES AND GOOD CLINICAL PRACTICE

## 13.1 Ethics and Good Clinical Practice

Sponsor personnel, CRO personnel, and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the "Declaration of Helsinki," and with the laws and regulations of the country in which the study is conducted.

## 13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the parent(s) / legally designated representative and the subject (such as the ICF and the assent form) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

## 13.3 Informed Consent

Pediatric subjects are legally unable to provide informed consent. Therefore, fully informed consent must be obtained from parent(s) or legally designated representative prior to enrolling the child into the study. The ICF(s) must be signed before performance of any study-related procedure/activity.

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from the parent(s) / legally designated representative of each individual participating in this study. Assent must be obtained from study participants who are developmentally capable. The criteria for developmental capability to give assent follows local requirements.

The ICF(s) and Assent(s) used must be approved by both the Sponsor (or delegate) and by the reviewing IEC/IRB and be in a language that the parent(s) or legally designated representative and the potential subject can read and/or understand.

The investigator/delegate must explain to parent(s) / legally designated representative that they are completely free to refuse to enter their child into the study, or to withdraw him/her from it at any time for any reason without having to provide any justification.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to the parent(s) or legally designated representative of potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. They will be informed that choosing not to participate will not affect the care the potential subject will receive. Finally, they will be told that the investigator will maintain a subject 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 and its partners personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the parent(s) or legally designated representative of the subject is authorizing such access.

Special attention shall be paid to the information needs of individuals, as well as to the methods used to give the information. Adequate time shall be given for the parent(s) or legally designated representative to consider their decision for their child to participate in the study and it shall be verified that they have understood the information (e.g., by asking them to explain what is going to happen).

Subjects who come of age during their study participation must be consented to continue their participation in the study. The age when subjects are considered capable to give informed consent must follow local regulations.

The ICF for parent(s) / legally designated representative, for subjects who come of age and the Assent Form for developmentally capable subjects will be provided in the country local language(s). Distinct assent forms are provided per age categories as per local practice.

If a female partner of a male participant becomes pregnant, an informed consent will be obtained prior collecting the information on pregnancy. For pregnant partners who are not yet of legal age, the consent will be obtained from parent(s)/ legally designated representative and assent will be obtained from the partner.

Site personnel authorized to participate in the consent/ assent process and/or to obtain consent/assent from the parent(s) / legally designated representative and subject will be listed on the Delegation of Authority form. A study physician must be available to answer medical questions or questions regarding alternative therapies.

The parent(s) / legally designated representative and/or subject who come of age must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated, and timed (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) by the authorized site personnel listed on the Delegation of Authority form.

A copy of the signed and dated ICF is given to the parent(s) / legally designated representative; the original is filed in the site documentation. Subjects who were assented receive a copy of the assent form; the original is filed in the site documentation. The informed consent process as well as the assent process must be fully documented in the subject's medical records. This must include the study reference, the subject number, the date and, if applicable, time when the subject's parent(s) / legally designated representative was first introduced to the Sponsor clinical study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject's parent(s) / legally designated representative, and any additional person present during the consent process (e.g., subject, any other family member), statement that a copy of the signed ICF has been given to the subject's parent(s) / legally designated representative. For subject(s) who come of age during study conduct the date the subject was first approached to consent to continue participation must be documented. In addition, all other information indicated for parent(s) /legally designated representative is also documented and the subject receives a copy of the signed and dated ICF.

In the case that the site would like to recruit subjects 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 subject's rights are respected and the consent obtained is legally valid. If the subject 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 subject is obtained. The CRO, the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before such subjects are recruited.

A subject who is scheduled for re-screening is not required to sign another ICF if the re-screening occurs within 90 days from the previous ICF signature date.

## 13.4 Compensation to Subjects and Investigators

The Sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject's parent(s) / legally designated representative in the event of study-related injuries will comply with applicable regulations.

## 13.5 Protocol Adherence/Compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform the CRO or its representative, in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to Sponsor or (overruling) local requirements.

All relevant protocol deviations will be reported in the CSR. IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

## 13.6 Protocol Amendments

Any change to the protocol can only be made through a written protocol amendment. A protocol amendment must be submitted to IEC/IRB and regulatory authorities, according to their requirements.

## 13.7 Essential Documents and Retention of Documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

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.

These records are to be classified into two different categories of documents: ISF and subjects' source documents.

These records must be kept by the investigator for as long as is necessary to comply with the Sponsor's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. 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 investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the CRO to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from the CRO. The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Should the investigator wish to assign the study records to another party, or move them to another location, the CRO must be notified in advance. 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; 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.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The printouts must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per the CRO's instructions. If it was not possible for the CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

## 13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by the CRO. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support, if applicable, should also be available during the SIV.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

The Sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study. During the study, the CRA will contact and visit the site

regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. The Sponsor monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The PI must ensure that the eCRF is completed after a subject's visit (site visit or telephone call), and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The investigator and required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

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.

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.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study-site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. In case a site does not enroll any

subjects, the close-out visit may be performed prior to study database closure at the discretion of the Sponsor.

## 13.9 Investigator Site File

Each site will be provided with an ISF prior to the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP Section 8.

The ISF will include a table of content listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from the CRO. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform the CRO during the course of the study, or the Sponsor if this applies after the end of the study.

If the PI will change, or if the site will relocate, the CRA must be notified as soon as possible.

## 13.10 Audit

The Sponsor's or the CRO's Global Quality Management (GQM) representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to the CRO's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities. Subject privacy must, however, be respected.

## 13.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform the CRO (usually via the CRA) that such a request has been made.

The investigator and site personnel must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

## 13.12 Publication Policy / Dissemination of Clinical Study Data

All information, including but not limited to information regarding macitentan or the Sponsor's operations (e.g., 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/assent.

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 CSR 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 CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Study subject 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 substudy 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.

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# 15 APPENDICES

## 15.1 Appendix 1: Child Pugh Classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to the following table [FDA 2003]:

**Table 8: Child Pugh Classification**

| | **Score** | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| Total bilirubin (mg/dL) | < 2.0 | 2.0-3.0 | > 3.0 |
| Serum albumin (g/dL) | > 3.5 | 2.8-3.5 | < 2.8 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy* | Grade 0 | Grade 1-2 | Grade 3-4 |
| Prothrombin time (seconds prolonged) | < 4 | 4-6 | > 6 |

*Hepatic encephalopathy scoring will be based on the following criteria:
• Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram
• Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
• Grade 2: lethargic, time disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
• Grade 3: somnolent, stuporous, place disoriented, hyperactive reflexes, rigidity, slower waves
• Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 3 cycles per second delta activity

- Class A: Score 5-6
- Class B: Score 7-9
- Class C: Score 10-15

## 15.2 Appendix 2: Instructions on Switch in ERA Treatment

**Transition from bosentan to macitentan:**

- Switching PAH treatment from bosentan to macitentan when a patient's clinical condition is unstable or undergoing continuous deterioration is not recommended.
- To ensure continuous ERA-based PAH therapy when switching patients from bosentan to macitentan, it is recommended to initiate macitentan on the day following the last dose of bosentan.
- Continued adherence to the Tracleer product label with respect to the potential for drug-drug interactions is recommended for a period of up to 7 days after the permanent discontinuation of bosentan.

## 15.3 Appendix 3: 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.

## 15.4 Appendix 4: Panama Functional Class for Pediatrics

**For children aged 0-0.5 years**

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 years**

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 (e.g., 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.

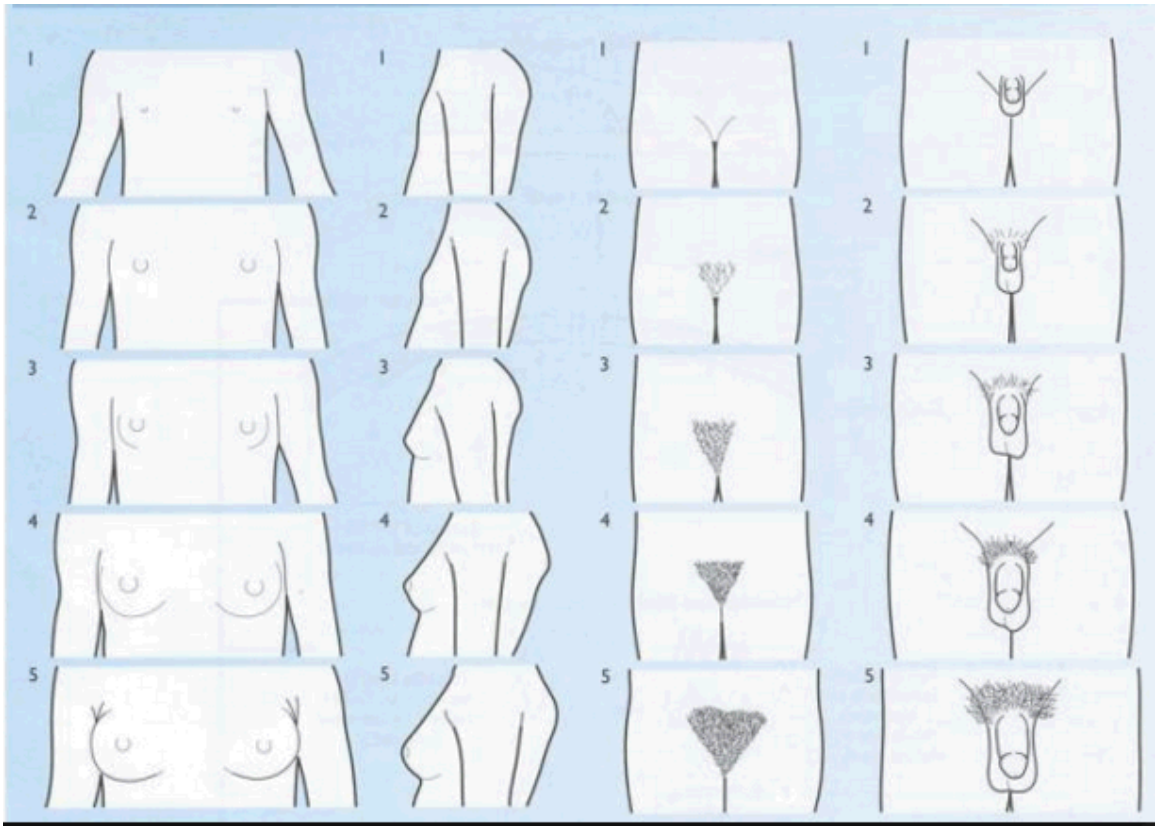
Class II Slight limitation of physical activity, unduly dyspnoeic and fatigued when playing with his/her classmates. Comfortable at rest. Continues to grow along own centiles. School attendance 75% normal. No chest pain.

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 (e.g., 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.

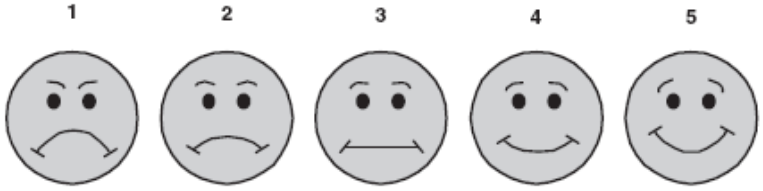
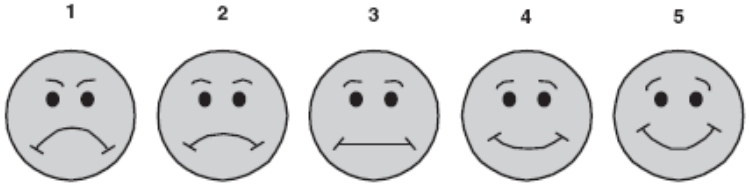
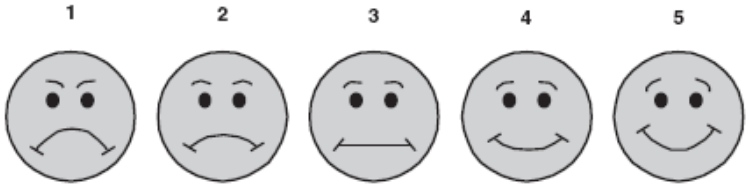
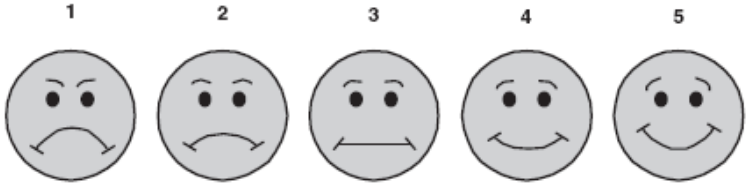
## 15.5 Appendix 5: Tanner Scale

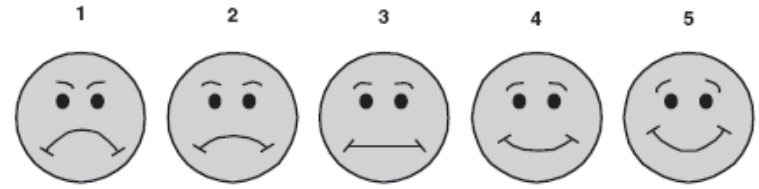



Illustrated by Michal Komorniczak (Poland)

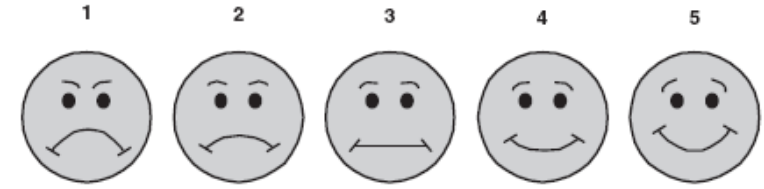
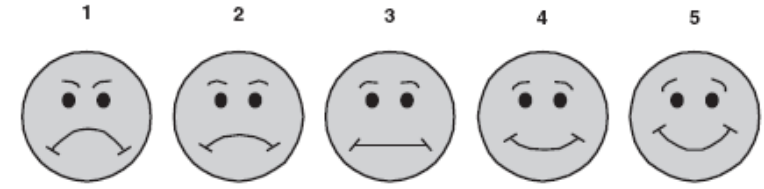
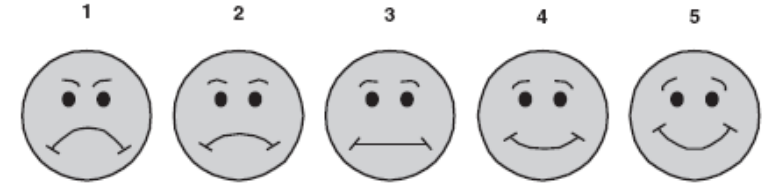
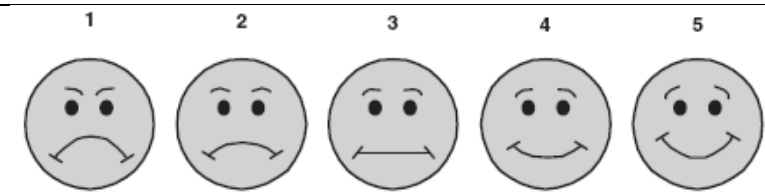
## 15.6 Appendix 6: Palatability and Acceptability of Macitentan

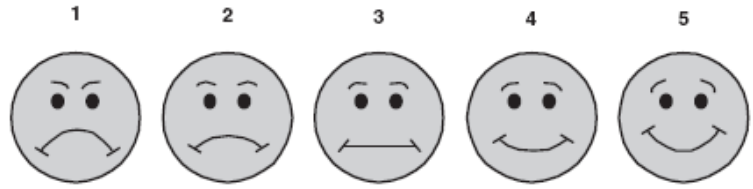
**ACCEPTABILITY AND PALATABILITY QUESTIONNAIRE FOR PARTICIPANTS**

| | | |
|---|---|---|
| 1. | How much do you like the taste of this medicine? |  <br>Dislike very much / Dislike a little / Not sure / Like a little / Like very much |
| 2. | How easily can you swallow this medicine? |  <br>Very difficult / Difficult / OK / Easy / Very easy |
| 3. | How much do you like that this medicine is taken once every day? |  <br>Dislike very much / Dislike a little / Not sure / Like a little / Like very much |
| 4. | How easily can you disperse the medicine? |  <br>Very difficult / Difficult / OK / Easy / Very easy |

| | | |
|---|---|---|
| 5. | How easy is it to remove the medicine from the packaging? |  |

**ACCEPTABILITY AND PALATABILITY QUESTIONNAIRE FOR CAREGIVERS**

| | | |
|---|---|---|
| 1. | On the basis of reaction/ facial expression of your child, how much do you believe your child likes the taste of this medicine? |  |
| 2. | On the basis of reaction/ facial expression of your child, how easily can your child swallow this medicine? |  |
| 3. | How much do you like that this medicine is given once every day? |  |
| 4. | How easily can you disperse the medicine? |  |

| | | |
|---|---|---|
| 5. | How easy is it to remove the medicine from the packaging? |  |

## 15.7 Appendix 7 :Short Form (SF)-15 Questionnaires

ID# _____

Date: _____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**TEEN REPORT** (ages **13-18**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**CHILD REPORT** (ages **8-12**)

PedsQL 2

ID#_____

Date:_____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**PARENT REPORT** for **TEENS** (ages **13-18**)

PedsQL 2

CCI

ID# _____

Date:_____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**PARENT REPORT** for **CHILDREN** (ages **8-12**)

PedsQL 2

ID# _____

Date:_____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**PARENT REPORT** for **TODDLERS** (ages **2-4**)

PedsQL 2

CCI

ID# _____

Date:_____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**PARENT REPORT** for **YOUNG CHILDREN** (ages **5-7**)

PedsQL 2

CCI

ID# _____

Date:_____

# PedsQL™

## Pediatric Quality of Life Inventory

Version 4.0 Short Form (SF15)

**YOUNG CHILD REPORT** (ages **5-7**)

PedsQL 2

CCI

CCI

## 15.8 Appendix 8: Cardiac Module Questionnaires

ID# _____

Date:_____

# PedsQL™
## Cardiac Module

Version 3.0

**TEEN REPORT** (ages **13-18**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™
## Cardiac Module

Version 3.0

**CHILD REPORT** (ages **8-12**)

PedsQL 2

CCI

ID# _____

Date:_____

# PedsQL™
## Cardiac Module

Version 3.0

**PARENT REPORT** for **TEENS** (ages **13-18**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™
## Cardiac Module

Version 3.0

**PARENT REPORT** for **CHILDREN** (ages **8-12**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™
## Cardiac Module

Version 3.0

**PARENT REPORT** for **TODDLERS** (ages **2-4**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™
## Cardiac Module

Version 3.0

**PARENT REPORT** for **YOUNG CHILDREN** (ages **5-7**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™
## Cardiac Module

Version 3.0

**YOUNG CHILD REPORT** (ages **5-7**)

PedsQL 2

PedsQL 3

## 15.9 Appendix 9: Multidimensional Fatigue Scale Questionnaires

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**TEEN REPORT** (ages **13-18**)

PedsQL 2

CCI

[redacted]

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**CHILD REPORT** (ages **8-12**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**PARENT REPORT** for **TEENS** (ages **13-18**)

PedsQL 2

CCI

[redacted]

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**PARENT REPORT** for **CHILDREN** (ages **8-12**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**PARENT REPORT** for **TODDLERS** (ages **2-4**)

PedsQL 2

CCI

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**PARENT REPORT** for **YOUNG CHILDREN** (ages **5-7**)

PedsQL 2

CCI

[redacted]

PedsQL 1

ID# _____

Date: _____

# PedsQL™

## Multidimensional Fatigue Scale

Standard Version

**YOUNG CHILD REPORT** (ages **5-7**)

CCI

PedsQL 2

CCI

[redacted]

PedsQL 3

## 15.10 Appendix 10 : Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. A Summary of previous amendments is provided below:

| Amendment | Date | Main reason(s) |
|---|---|---|
| Amendment 7, Version 8 | 25 Jan 2021 | It has been clarified which sponsor team members are blinded to treatment assignment in this open-label study. Reference has been made to the Firewall Charter which is in place since study start and which governs the flow of blinded and unblinded data.<br><br>The background information on macitentan safety data has been updated to match the Investigator's Brochure (IB). Language for the definitions and the reporting of serious adverse events (SAE) has been updated. |
| COVID-19 Appendix, Version 1 | 17 Jun 2020 | To provide a guidance on study conduct during the COVID-19 pandemic. |
| Amendment 3.1, Version 4.1 | 17 Jul 2020 | This amendment constitutes an urgent safety measure and will be implemented with immediate effect.<br><br>The rationale for this urgent safety measure is a newly identified drug-drug interaction (DDI) between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 & CYP2C9). Per Physiologically Based Pharmacokinetic (PBPK) model, fluconazole (400 mg daily) co-administration could result in a 3.8-fold increase in macitentan exposure due to the dual inhibition of the two most important metabolic pathways. |
| Amendment 5, Version 6 | 10 Jun 2020 | The synopsis of the global protocol Version 5 (dated 20 March 2020) was inconsistent with the core text in Section 4.4 Exclusion Criteria (numbers 16 and 18), and the Extension study was accidentally deleted in protocol Section 3.1. Therefore a new protocol version 6 (dated 10 June 2020) is issued to correct these inconsistencies. The rationale for changes from Protocol Version 4 are copied in this section since Protocol Version 5 will not be submitted for approval by Health Authorities and independent Ethics Committees / Review Boards. |

| | | |
|---|---|---|
| | | Changes introduced in protocol Version 5 dated 20 March 2020:<br><br>• In order to improve subject retention in this long-term controlled study especially for subjects without endothelin receptor antagonist in their background therapy the following changes are applied to the protocol:<br>  ◦ Macitentan will be offered to all subjects after Clinical Event Committee (CEC)-confirmed disease progression, including the subjects in the standard of care (SoC) group, if this is in the subject's best interests per their investigator's judgment. In order to reduce potential reporting bias for disease progression in the SoC group, macitentan will only be offered after the event has been confirmed by the blinded CEC.<br>  ◦ The information regarding the option to cross over to macitentan has also been added to the informed consent forms and to the assent form for adolescents.<br>  ◦ The planned statistical analysis has been modified for key secondary variables, exploratory variables and safety variables, to account for cross-over to macitentan in the SoC arm, after CEC-confirmed disease progression. The analysis of recurrent events (e.g., CEC-confirmed disease progressions and hospitalizations for PAH) as well as the description of the number of days hospitalized have been deleted due to the cross-over to macitentan in the SoC arm, which makes the interpretation of results too difficult.<br>• In addition, the study population will be extended to patients diagnosed with pulmonary arterial hypertension (PAH) more than 5 years before randomization (i.e., there will be no limitation with regard to time since diagnosis) since it is assumed that these patients are at similar risk of developing disease progression as patients diagnosed within 5 years of study entry.<br>• The 6-minute walk distance (6MWD) will be added as an exploratory endpoint in children ≥ 6 years of age, |

| | | |
|---|---|---|
| | | who are able to understand and perform the test, in order to enrich the collected data with exercise capacity.<br>• A clarification to the Exclusion criterion No.16 has been added in order to clarify for which patients the Child Pugh Score must be fully documented.<br>• An additional exclusion criterion for renal insufficiency has been included in the protocol in order to be consistent across macitentan trials.<br>• Clarifications and minor corrections have been added to the protocol.<br><br>Non-substantial changes introduced in Protocol Version 6 dated 10 June 2020:<br>• Exclusion criterion No. 16 and No. 18 have been adjusted in the protocol synopsis to match Section 4.4 of the core protocol text.<br>• The paragraph regarding the planned Extension study, which was accidentally deleted in Section 3.1 of Protocol Version 5, has been reinserted.<br>• Publications not referred to have been removed from Section 14. |
| Amendment 4, Version 5 | 20 Mar 2020 | This document was only submitted to the US FDA. Subsequently inconsistencies were detected between the protocol synopsis and the protocol core text. It was decided to correct those inconsistencies and release Protocol V6 for submissions.<br><br>The changes are summarized in Amendment 5, Protocol Version 6. |
| Amendment 3, Version 4 | 13 Mar 2018 | Feedback received from study investigators during the site initiation visits has been taken into account to improve the feasibility of the study protocol.<br><br>• The overnight hospitalization during the pharmacokinetic (PK) substudy visit has been changed to a recommendation since it poses an unnecessary burden to pediatric participants.<br><br>• PK substudy visit can occur any time during steady-state conditions to improve enrollment in |

| | | |
|---|---|---|
| | | the PK substudy and potentially allow earlier completion.<br>• Monthly pregnancy tests can be taken at home under supervision of parents/caregiver/guardian in order to reduce the burden to study participants. The investigator must confirm via phone that test was performed and verify the results.<br>• Collection of accelerometry data has been reduced from two weeks to 10-14 days in order to ease the burden on participants while keeping the risk of missing data low. The data can be collected after study visit if they could not be collected before the visit in order to reduce the risk of missing data.<br>It has been clarified that analysis of PK data will be done regularly in order to confirm the appropriateness of the selected dosing regimen.<br>The safety follow-up call has also been added for subjects in the Standard of Care (SoC) group in order to collect the same level of safety data in both treatment arms. In addition, the definition of end of SoC has been added to define start of safety follow-up period.<br>Instructions have been appended [Appendix 2] for the switch of an endothelin receptor antagonist to macitentan after randomization in order to standardize procedures across all sites.<br>Monthly pregnancy tests also apply to participants with tubal sterilization since this method cannot completely prevent occurrence of pregnancy.<br>The study endpoints and statistical analysis sections have been aligned with the Statistical Analysis Plan (Final Version 1, 9 August 2017), which was finalized before the randomization of the first subject.<br>The PK bioanalysis has been delegated to PRA Health Sciences and respective corrections have been made to the protocol. |

| | | |
|---|---|---|
| | | Minor clarifications and corrections have been added to the protocol.<br><br>Some of the above changes have also affected the informed consent/assent forms. In addition, the assent form documents for children have been merged as listed below in order to reduce the administrative burden:<br><br>• Assent forms for children aged 7–9 years and 10–12 years merged into one assent for children aged 7–12 years<br><br>• Assent forms for adolescents aged 13–15 years and 16–17 years merged into one assent for adolescents aged 13–17 years |
| Amendment 2, Version 3 | 25 Apr 2017 | In January 2017, the FDA raised concerns regarding the protocol, which were addressed in the Type A meeting held on 21 March 2017. This meeting led to enhancements of the study protocol as follows.<br><br>• In order to render the study population more homogeneous (etiology-wise), and similar to the adult population evaluated in the SERAPHIN adult study, the subjects with pulmonary arterial hypertension (PAH) associated with Eisenmenger syndrome or with inoperable left-to-right shunts will be excluded.<br>• Patients with PAH associated with congenital heart disease who have co-incidental shunts are eligible. Their hemodynamic data will be centrally reviewed for eligibility before randomization.<br>• The rationale for a target treatment effect of hazard ratio (HR) = 0.65 for macitentan vs Standard of Care (SoC), used in the sample size assumptions, is clarified. A HR = 0.65 was chosen to account for 50% on planned/ongoing ERA at randomization.<br>• In order to increase the interpretability of a study comparing macitentan vs a SoC control group containing other ERAs:<br>o The enrollment of subjects with an SoC control group, containing other ERAs, is limited to 40% of the overall number of randomized subjects as per |

| | | |
|---|---|---|
| | | Interactive Response Technology. The choice of a cap to 40%, as compared to the original sample size assumptions (50%), will allow having a higher power and, as such, the ability of the study to deliver interpretable results.<br>o The randomization and the primary analysis are stratified, by ongoing/planned ERA treatment (yes vs no) and WHO FC (FC I/II vs FC III) at randomization.<br>• The rule for futility recommendation has been modified to increase the likelihood of the study conclusiveness. In addition to the current futility boundary (HR > 0.80), the Independent Data Monitoring Committee will consider stopping for futility, if the lower boundary of the 95% (2-sided) confidence interval (CI) of the observed HR exceeds 0.65.<br>o This additional rule does not affect the type I error spending and also allows for the exclusion of an overall treatment effect of HR = 0.65 for macitentan vs SoC at the interim analysis.<br>o The probability of stopping early for futility is decreased by the additional rule and is changed accordingly in Table 8 of the sample size section.<br><br>In addition, the Sponsor, through the Voluntary Harmonization Procedure (VHP) assessment number 983 (VHP2016117), was advised to extend the current benefit-risk analysis to contain further information on the long-term safety of macitentan in children and adolescents.<br><br>Furthermore, the Sponsor, was advised by the Portuguese Health Authorities (INFARMED) to ensure collection of adverse events leading to discontinuation of treatment in both treatment groups.<br><br>To account for a pediatric population, it is considered more appropriate to use pulmonary vascular resistance index instead of pulmonary vascular resistance for PAH definition, since it takes into account the body surface area |

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| | | as recognized by the most recent pediatric guidelines [Ivy 2013, Abman 2015, Hansmann 2016].<br><br>Feedback received from study investigators during the investigator meeting has also been taken into account, mostly to improve the feasibility of the study protocol. This feedback lead to the following:<br><br>• Change of entry criterion time since diagnosis of PAH from 12 months to 5 years before randomization<br>• Downtitration of prostanoids as per local practice in subjects randomized to macitentan instead of requesting their immediate stop<br>• Allowing removal of the accelerometer device during night rest<br>• Allowing self-assessment of pubertal Tanner stage by parents or subjects<br>• Allowing Contract Research Organizations (CROs) to collect monthly blood/urine samples at subject's home<br>• Allowing that quality of life questionnaires are answered at home by the parent<br>• Requesting serious adverse events and Pregnancy forms to be sent to CROs for treatment blinding<br>• Clarifications to several sections<br><br>In addition, contact details of contracted CROs have been added to the Contract Research Organizations Information. |
| Amendment 1, Version 2 | 13 Oct 2016 | The sponsor, through the Voluntary Harmonization Procedure (VHP) assessment number 2016117, was advised to clarify that pharmacokinetic (PK) substudy data will be used to update the PK model, and which methods of contraception are highly effective. For this reason the protocol has been amended.<br><br>In addition, the following clarifications and corrections have been made:<br><br>• For the diagnosis of pulmonary arterial hypertension (PAH), pulmonary artery wedge pressure (PAWP) is requested to exclude increased left heart pressures as |

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| | | the cause of pulmonary hypertension. Since PAWP and left ventricular end diastolic pressure (LVEDP) are both surrogates for left atrial pressure (LAP), LVEDP or LAP can replace PAWP for the diagnosis of PAH, refer also to Section 1.1.1 of the protocol.<br>• The assessment of cardiac and fatigue components of quality of life will only be assessed in English-speaking subjects in the USA, since they have not been validated for other countries and languages.<br>• Only events denoting disease progressions will be exempted from expedited reporting to health authorities, IECs/IRBs and investigators.<br>• Adverse events leading to study drug discontinuation will be only described for the macitentan arm since no study drug is administered in the control arm.<br>Furthermore, for completeness the acceptability and palatability forms as well as the quality of life questionnaires have been appended to the protocol. |

## 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: Actelion Pharmaceutical Ltd and Janssen Research and Development, a Division of Janssen Pharmaceutica NV

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 [redacted] | 24-Nov-2021 14:58:48 (GMT) | Document Approval |

**Actelion Pharmaceutical Ltd**
**Janssen Research & Development***

**Clinical Protocol**

**COVID-19 Appendix**

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**Protocol Title**

A Multicenter, Open-label, Randomized Study with Single-arm Extension Period to Assess the Pharmacokinetics, Safety and Efficacy of Macitentan Versus Standard of Care in Children With Pulmonary Arterial Hypertension

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**TOMORROW**

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**TOMORROW: pediaTric use Of Macitentan tO delay disease pRogRessiOn in PAH Worldwide**

**Protocol AC-055-312; Phase 3**

**ACT-064992 (JNJ-67896062) macitentan**

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC; or Actelion Pharmaceuticals Ltd. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

**EudraCT NUMBER:** 2016-001062-28

**Status:** Approved

**Date:** 16 November 2021

**Prepared by:** Actelion Pharmaceuticals Ltd (a Janssen Pharmaceutical company of Johnson & Johnson)

**EDMS number:** EDMS-RIM-265698, 5.0

**THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL**

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

# COVID-19 APPENDIX

## GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related subject 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 subjects and site staff. If, at any time, a subject's safety is considered to be at risk, study treatment will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects 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 subjects on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the subject, 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 electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

## CHANGES TO STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The sponsor evaluates the benefit-risk of study continuation for study subjects with planned upcoming study interventions (eg, onsite visits, investigational product dispensing). The available safety information for the respective subject will be considered. If needed (eg, in case of missing safety information), the sponsor will discuss individual cases directly with the responsible investigator.

**Screening of New Subjects**

- Screening of new subjects is only allowed if, in the investigator's judgment, study visits can occur onsite and approval is provided by the sponsor.
- Subjects who are in Screening and for whom onsite visits per protocol cannot occur due to COVID-19 restrictions must be considered screen-failed. Subsequent care for screen-failed subjects remains the investigator's responsibility following local guidelines.
- Re-screening of screen-failed subjects is allowed if TOMORROW entry criteria are met after COVID-19 restrictions are lifted and onsite visits can resume safely.

**Scheduled Visits**

- When scheduled onsite visits can take place, all assessments per protocol will be performed, unless in the investigator's judgment the assessment is not safe either for the subject or for the site staff. If blood samples (hematology and/or clinical chemistry) cannot be analyzed at the central laboratory due to COVID-19-related impact, the samples will be tested locally.
- When COVID-19-related local restrictions do not allow onsite visits, investigators will schedule virtual visits (ie, via phone or video call) within the requested visit window per protocol (ie, every 12 weeks ±2 weeks) in order to collect the following data for entering into the eCRF:
  - Pulmonary arterial hypertension (PAH) signs and symptoms (to check for disease progression)
  - WHO & PANAMA Functional Class (FC) (to check for disease progression)
  - Adverse events
  - Concomitant therapies
  - Childbearing potential (where applicable)
  - Counseling for contraception (where applicable)
  - Monthly pregnancy tests (where applicable)
  - Quality of Life questionnaire (if applicable)
  - Study treatment compliance
  - Palatability and acceptability of macitentan (if applicable).

  In addition, the investigator will remind study subjects to wear the accelerometry device (if applicable for a visit) per protocol.

The investigator will record in the source document how the above-mentioned data have been obtained (eg, in-person, via video call, via phone call).

If any of the above-mentioned assessments are missing for a visit where the assessments are planned per protocol, or if a visit is performed outside the protocol-specified time window, a protocol deviation will be assigned using the prefix "COVID-19-related". Visits performed virtually will also be documented in the clinical trial management system (CTMS) as a protocol deviation using the prefix "COVID-19-related".

- If an onsite visit is not feasible due to COVID-19 restrictions, blood samples can be collected locally (ie, by flying nurse [contract research organization], site personnel, or by a local healthcare professional, including local laboratory).
- If any blood samples are analyzed locally, a copy of the local laboratory certification and the respective reference ranges must be obtained and stored in the Investigator Site File (refer to Section 7 of the protocol).
- If the subject is visiting a local healthcare professional, the investigator will ask the local healthcare professional to share the following data (if available) for eCRF data entry:
  - Hematology and clinical chemistry blood test results with normal ranges (including re-tests as per Section 5.1.10 of the protocol)
  - NT-proBNP test results with normal ranges
  - Vital signs (blood pressure/heart rate)
  - Monthly pregnancy test
  - Weight and height
  - Physical examination
  - Tanner staging.

  The investigator will collect a copy of the respective local report(s) including above-mentioned assessments and will sign and date the report(s) to confirm the content was reviewed and assessed for potential adverse events. These reports will serve as source documents for the TOMORROW study.

  Collection of data via local healthcare professionals will be documented in the CTMS as a protocol deviation using the prefix "COVID-19-related".

  If applicable, the home pregnancy test kit will be provided by the site (eg, shipped directly to the subject's family), or the subject's family may purchase the home pregnancy test locally, if shipment is not feasible.

**Investigational Product (IP)**

- Where COVID-19-related local restrictions do not allow onsite visits, the investigator will consult the sponsor to discuss the possibility of direct-to-patient (DTP) shipment of study treatment (macitentan and Standard of Care [SoC]) via courier. Available safety data (assessed by the investigator and/or local health care professional) will be reviewed to verify that no treatment interruption/discontinuation criteria have been met (refer to Section 5.1.10 of the protocol). Local regulations for DTP shipment will be followed.

- The investigator may also ask the sponsor to support DTP shipment of SoC medication and of phosphodiesterase type 5 inhibitor (eg, sildenafil, tadalafil).
- In case of DTP shipment of IP, the investigator will use the latest available body weight assessment by a healthcare professional to assign the macitentan kit in Interactive Response Technology (IRT).
- If needed, it will be discussed on a case-by-case basis between the investigator and the sponsor whether the number of IP kit packages to be shipped to the subject will cover the 12-week interval between scheduled visits (as per protocol) or less or more.
- An investigator's site (not the sponsor) will ship the IP or SoC to the subject. The investigator will contact the subject's family for consent to provide their name and address to the courier as per local COVID-19 guidance.
- The IP shipment should be made in a manner that allows tracking of transport, delivery, receipt and temperature control (refer to Janssen COVID-19 DTP Process). When IP is shipped by study sites, the receipt and return of IP must be documented in order to assess compliance and accountability, per protocol.

Study treatment interruption or discontinuation due to COVID-19 will be reported as protocol deviations using the prefix "COVID-19-related".

**Informed Consent**

- Where required, informed consent for COVID-19-related changes in study conduct must be obtained per local COVID-19 guidance (eg, retrospective written consent may apply). Assent from children/adolescents will not be requested for these changes unless specifically requested by local regulations related to COVID-19.
- The investigator will inform families of subjects with planned site visits or scheduled assessments during COVID-19 restrictions about changes and alternatives to standard visit procedures (eg, virtual visits, assessment through local healthcare professionals, DTP drug shipment). The date, means of communication (eg, via email, or virtually via phone/video call), and consent received will be documented by the investigator in the source data. The options discussed and the agreed solution as well as questions and concerns addressed will also be documented by the investigator.
- In case of DTP shipment (eg, IP, pregnancy tests), parent/legal guardian (or subject who came of legal age) must consent to having their personal data shared with the courier company.
- All attempts made by the study site staff to reach the subject's family during COVID-19 restrictions must be documented.

**Site Monitoring**

- If onsite monitoring is not possible due to COVID-19 restrictions, monitoring will be done remotely to the extent possible. Changes to the monitoring process will be documented in the monitoring plan. Onsite monitoring will be delayed until after COVID-19 restrictions are lifted.
- In order to catch up with source data verification and resolution of potential pending issues, onsite monitoring visit frequency and/or duration may be increased after COVID-19 restrictions are lifted.

**Audits**

- During the COVID-19 pandemic at the impacted sites, clinical site Good Clinical Practice audits with direct impact/engagement with the clinical investigator team will not be conducted to comply with national, local and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement, if possible.

## STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

- Study participants can undergo a COVID-19 vaccination procedure in compliance with applicable local governmental regulations.
- No pharmacokinetic interactions between the study intervention and currently available COVID-19 vaccines are expected. In addition, based on the mechanism of action of the study intervention and COVID-19 vaccines, no relevant interaction is expected.
- Any COVID-19 vaccine administered to a study participant is considered a concomitant medication and should be reported on the electronic case report form (eCRF).
- For serious adverse events (SAEs) reported after COVID-19 vaccination, the investigator should provide narrative details on the SAE form to allow adequate assessment of causal relationship between the reported SAE and vaccination. This is particularly relevant in cases where the reported SAE is an expected event with the study intervention and the COVID-19 vaccine. If the event is serious and considered to be related to both the COVID-19 vaccine and the study intervention, it is a serious adverse reaction and expectedness must be assessed. Suspected unexpected serious adverse reaction (SUSAR) reporting will be performed if the serious adverse reaction is unexpected as per applicable reference safety document.
- Study participants do not require unblinding of the study intervention to receive a COVID-19 vaccine.

## 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: Actelion Pharmaceutical Ltd and Janssen Research and Development, a Division of Janssen Pharmaceutica NV

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 | 16-Nov-2021 12:46:04 (GMT) | Document Approval |
| PPD | 17-Nov-2021 08:37:22 (GMT) | Document Approval |