Janssen Research & Development

Statistical Analysis Plan for Core Period of Study

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

Protocol AC-055-312/TOMORROW
Version 5.0
Macitentan (ACT-064992)

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

Author	PPD
Reviewer	
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VERSION HISTORY

Table 1: SAP Version History Summary

Version	Effective Date	Reason
1.0	14-OCT-2016	New
1.1	02-NOV-2016	Updated after statistical peer reviews
1.2	12-DEC-2016	Updated after clinical review
1.3	31-JUL-2017	Updated after protocol amendment 3
1.4	31-MAR-2020	Updated after protocol amendment 4
1.5	07-APR-2020	Updated after protocol version 5
1.6	05-JUN-2020	Updated after protocol version 6
2	12-NOV-2020	Updated after protocol version 7
3	30-MAY-2022	Updated after protocol version 9
4	22-DEC-2022	Updated to add details necessary for statistical programming
5	14-MAR-2023	Updated to add details necessary for statistical programming

AMENDMENT HISTORY

Version 5
This Statistical Analysis Plan was amended before the analysis 1 SDTM release (before the unblinding of blinded team members) to add details needed for programming. • Macitentan/SoC discontinuation and study withdrawal definitions have been optimized • AESI definitions updated to MedDRA v25.1 • AETERMs to select AEs of interest related to COVID-19 added • Clarification on laboratory values below or above the limit of quantification added • Clarification on PK Set 2: it will not be calculated for the analyses generated by this SAP • EOM, EOSoC, End-of-Randomized-Treatment, EOCP and EOS handling of missing dates have been optimized • Clarification of calculation of age and weight categories to be used for primary endpoint added • BMI formula added • Clarification on Planned/ongoing SoC at randomization as per IRT questions added • Clarification added for time-to-event endpoints for crossover subjects

Version 4

This Statistical Analysis Plan was updated to add necessary details for statistical programming.

- It has been specified that this SAP version is used only in countries where Protocol V9.0 is approved.
- End of Core Period definition has been modified to incorporate handling of missing data.
- It has been clarified that exploratory p-values are shown for all Analyses but no formal hypothesis testing is done.
- The following variables were added to the Subject Disposition table:
  - Applicable to all subjects: "Subjects who are lost to follow-up in the single-arm extension study", "Subjects who completed the study", "Subjects enrolled in single-arm extension study";
  - Applicable to subjects < 2 y.o.: "Subjects enrolled (assigned to macitentan and with enrollment date in the IRT system)".
- A method to assign Countries to Regions was added.
- It was specified that the ATC Level used to assign PTs is Level 4.
- Previous therapies have been defined based on randomization date instead of informed consent date. Concomitant therapies (general and PAH-specific) have been defined based on the different periods of analysis.
- The definition for SoC discontinuation has been updated.
- It has been specified that premature study visit discontinuations due to natural disaster, major disruption or pandemic are identified with specific prefix in the reason for study visit discontinuation in the eCRF.
- The following endpoints definitions were updated as follows:
  - For Time to first CEC-confirmed disease progression, it was specified that in case of concomitant events happening on the same day, the first one in hierarchical order is summarized.
  - The EOCP imputation rule for Time to CEC-confirmed death due to PAH for subjects who have discontinued prematurely regular study visits during the core period was changed to the last survival follow-up contact;
  - A definition for the absolute change from baseline in plasma NT-proBNP was added and the unit of measure for plasma NT-proBNP was changed from pg/mL to pmol/L;
  - It was specified that, for crossover subjects, only values collected up to start of macitentan are considered for mean daily time spent in moderate to vigorous physical activity, quality of life variables and six-minute walk distance;
  - For echocardiography variables:

  - A formula to derive BSA-normalized TAPSE was added and unit of measure was changed from cm/m^2 to mm/m^2;
  - It was specified that both diastolic and systolic LVEI are analyzed.

- The following specifications have been included for the Quality of life variables:
  - It has been specified that, in the PedsQLTM Multidimensional Fatigue Scale questionnaire, only the General Fatigue Component is used and that, in the PedsQLTM 3.0 Cardiac Module, only the Heart Problems and Treatment Component is used;
  - It has been clarified that the Quality of life variables of interest are the total scores across all ages (and by age group for the PedsQLTM Generic Core Scales Short Form), separately for parent/caregiver reports and for subject reports, expressed as change from baseline.
  - It has been specified that the total scores are derived as per the PedsQLTM Scoring Manual and that the answers to each question are reverse scored and a higher score indicates better health.
- Derivation rules for Physical Activity variables have been included:
  - It has been specified that the mean daily time spent in Physical Activity as measured by accelerometry is expressed in minutes;
  - A formula has been added for both mean number of hours of daytime activity and mean count per minute of daily activity;
  - Thresholds for light and moderate to vigorous Physical Activity were specified;
  - It has been clarified that the variables used for the derivations are the ones excluding epochs when the device was not worn and that only days where at least 7 hours of data are recorded are considered for the derivations.
- The following endpoints were updated to add key timepoints of assessment:
  - Proportion of subjects with WHO FC I or II (yes/no) at Week 12;
  - Percent of baseline in plasma NT-proBNP at Week 12.
- Safety variables section has been updated as follows:
  - It has been clarified that safety variables are defined based on the treatment periods and treatment emergent period has been changed to Main treatment period throughout the document.
  - A definition for AEs with fatal outcome and AEs related to macitentan has been included.
  - TEAE wording has been removed;
  - It has been specified that the AEs of interest related to major disruption/natural disaster/pandemic are identified also by the words “REGIONAL CRISIS”.
- It has been clarified that death and primary cause of death are captured in a dedicated CRF form.

- Time to first Marked Laboratory Abnormality analyses have been removed.
- Analysis Sets updated:
  - PK Analysis Sets definition and usage were set as per protocol;
  - Definition of Safety Analysis Set 3 was updated to include also crossover subjects;
  - SAS3 is used for all listings of safety variables.
- Race subgroups have been changed to White vs Black or African American vs. Asian vs. Other.
- A definition for the Regular Visits has been included.
- General statistical methodology and definitions have been modified as follows:
  - It has been clarified that summaries are produced if 5 or more participants are enrolled in the analysis set.
  - It has been specified that summaries, graphs and the repeated measures mixed model include all scheduled timepoints up to Week 48, while the subsequent ones are only displayed if at least 10% of the subjects in the macitentan arm have a corresponding value.
  - It has been specified that listings are produced on FAS3/SAS3, but additional listings on FAS2/SAS2 may be requested ad hoc and specified in the DPS.
  - A definition for enrollment date was added.
  - The definitions for End-of-Macitentan date, End-of-SoC date, End-of-Core-period date and End-of-Randomized-Treatment date / Last intake of randomized study drug date have been updated.
  - It has been specified that, for Kaplan-Meier estimation, the median time to event is expressed in months and the derivation rule has been included.
  - For the stratified logistic regression, the code has been updated and it was specified that the model is used for WHO FC I or II endpoint only.
  - For the repeated measures mixed model, the code has been updated and the order of variance-covariance matrix in case of convergence problems has been included; it has been clarified that the mixed model estimates are displayed only at time points of interest.
- Statistical analyses have been updated as follows:
  - For Subject Disposition tables, it has been specified that also the number of subjects ongoing at Screening at the time of data cut are shown and that an additional disposition output for subjects <2 years old is produced.
  - Summaries and listings for minor PDs related to natural disaster/major disruption/pandemic have been removed.
  - Summary of subjects in the SAS3 has been added to the analysis.
  - It has been specified that other baseline characteristics are not summarized on

PK1 set and are listed only within the global QoL and physical activity listings.

- It has been specified that medical history is not summarized on PK1 set.
- It has been clarified that the number and percentages of randomized subjects ≥ 2 years old and of enrolled subjects < 2 years old receiving macitentan is provided by country and site, based on the FAS1 and FAS2 respectively.
- A summary of the number of subjects with at least one record of non-compliance (at least one reason present) on SAS3 has been included.
- Analysis sets for drug accountability and compliance have been changed from FAS to SAS.
- It has been clarified that study-drug concomitant therapies are summarized by ATC classification system and PT on the PK set 1, on the Subset of Crossover Subjects in the FAS1 and on FAS2 overall, and on the FAS1 by treatment group; and that PAH-specific concomitant therapies are summarized by PT on the FAS2 overall, and on the FAS1 by treatment group.
- A listing with macitentan exposure data for all subjects on the SAS3 has been added, while the duration of treatment listings on SAS1 and SAS2 have been removed.
- It has been clarified that the listings for subjects who prematurely discontinued randomized macitentan or SoC or non-randomized macitentan are run on SAS3, while listing for crossover subjects discontinuing macitentan is on SAS1. It was also specified that a flag is added to the listings for subjects discontinuing macitentan due to natural disaster, major disruption, or pandemic and subjects who had a first confirmed disease progression event.
- It has been specified that duration of time on regular visits is shown in weeks and summarized on the FAS3 (by treatment group and overall) and on the FAS2 (overall) separately.
- It has been specified that duration of time on study is shown in weeks and summarized on the FAS3 and on the FAS2 separately, by treatment group and overall.
- It has been specified that the duration of time on study is listed together with the duration of time on regular study visits.
- It was clarified that withdrawals due to natural disaster, major disruption or pandemic are not listed separately but flagged on the general listing.
- It has been specified that trough plasma concentrations of macitentan and ACT-132577 at Week 12 (subjects ≥ 2 y.o.) and Week 4 (subjects < 2 years old) are summarized by body weight, age group and overall for subjects ≥ 2 y.o. and by age group only for subjects < 2 y.o., and that also the coefficient of variation is displayed.
- It was specified that for Demographics, baseline characteristics and AEs, the used subgroups age, sex and race (not for all subgroups anymore).
- The Cox regression model has been removed from supportive analyses for the

time to CEC-confirmed disease progression.

- A sensitivity analysis using the stratification factors as collected in the eCRF (WHO FC) or gathered from PDs (ERA treatment ongoing/planned) has been added for the time to CEC-confirmed disease progression.
- It was clarified that for descriptive analyses on FAS2 only listings are provided.
- Concordance analysis for the nature and onset date of first disease progression has been changed to concordance analysis for the type of first disease progression and the descriptive analysis for time to event for subjects < 2 y.o. has been removed. It was clarified that median time to censoring and premature discontinuation are expressed in months.
- It has been clarified that the analysis of other secondary variables are carried out on the FAS1 and consider values collected up to the end of randomized macitentan or SoC + 7 days, or up to start of macitentan for crossover subjects, and that the analyses are only descriptive for subjects of the FAS2.
- For WHO FC I/II endpoint, it was specified that the logistic regression is only performed on Weeks 12 and 24 and an imputation rule was added for Week 12.
- For WHO FC I/II and Panama FC I/II endpoints, a shift table for changes from baseline at each time point on the FAS 1 and FAS2 and a histogram showing the percentage of subjects with functional class I or II at each time point on FAS1 have been added.
- For percent of baseline in NT-proBNP analysis, mean daily time spent in moderate to vigorous physical activity and other physical activity variables, and for Changes from baseline in QoL total scores, it has been specified that the model without treatment by visit interaction is re-run regardless of significance of the interaction term.
- For percent of baseline in NT-proBNP analysis, it has been specified that also change from baseline at each timepoint of assessment is descriptively summarized on FAS1 and FAS2 separately.
- It was clarified that the change from Baseline to Weeks 12 and 24 in echocardiographic variables are summarized descriptively also on the FAS2.
- For six-minute walk distance and other physical activity variables, descriptive statistics on FAS1 have been added.
- A definition of baseline for crossover subjects was added.

- Analysis of safety variables was modified as follows:
  - It was specified that summaries are provided by treatment group on SAS1 and overall on SAS2 and for crossover subjects.
  - Adverse Events section was streamlined by replacing description of different analyses with Table 6 describing all the AE analyses per type and by period.
  - It was specified that mostly all AEs are summarized for the “Overall core period” and “Main treatment period” for all subjects and for the “Post-crossover to macitentan period” for crossover subjects.

  - It was specified that the summary tables by SOC and PT and by PT are presented in descending order of incidence in the macitentan arm.
  - Laboratory tests are only summarized for the "Main treatment period" for all and for the "Post-crossover to macitentan period" for crossover subjects.
  - Pre-event core period was deleted as period of interest for safety analysis.
  - Kaplan-Meier estimates of the time to first AESI and to the first marked abnormalities have been removed from the analysis.
  - For analysis of deaths, it was specified that for both summaries and listings the period of analysis is from randomization (Visit 2 for subjects < 2 y.o.) until EOCP or cut-off date, whichever occurs first.
  - It was clarified that summary tables of number of subjects who died with primary cause of death are presented by descending order of PT according to the incidence of deaths in the macitentan arm.
  - A listing of deaths due to COVID-19 infection has been added to the analysis.
  - It was specified that, for vital signs and growth variables, only values collected up to end of randomized macitentan or SoC + 30 days, or up to start of macitentan for crossover subjects are considered, while for subjects < 2 y.o. values collected until end of macitentan treatment + 30 days are considered.
  - Descriptive summaries of changes from baseline in BP and heart rate on SAS2 have been added, while summaries of absolute values have been removed.
  - Scatter plots for worst post-baseline values versus baseline for laboratory data and eDISH plots were removed from the analysis.
  - Summary of absolute values and changes from baseline and plots of profile over time for erythrocyte count have been added.
  - The links to sex-specific standard growth percentiles has been added.
  - Summaries for childbearing potential have been removed.
  - Sexual maturation as measured by the Tanner stage is only summarized by treatment group on SAS1.
  - Period of analysis has been added for sexual maturation and childbearing potential.

- For QoL variables, the following updates were done:
  - Period of analysis definition was updated to consider crossover subjects.
  - Specified that box plots of QoL total score variable profiles over time are only provided for the PedsQLTM 4.0 Generic Core Scales Short Form (SF15) and that they are provided both by age group and overall
  - Spider plots for QoL variables have been removed.
  - A listing for QoL component score variables has been added on the FAS1.
  - It has been specified that QoL variables are analyzed separately depending on

subjects or caregivers report across age groups and overall.

  - It has been specified that the mixed model for changes from baseline in QoL total scores is performed separately by subjects or caregivers report.
  - It has been specified that palatability and acceptability are also summarized on SAS2 and listed, and that, for this endpoint, no distinction is done between subjects/caregiver evaluations (assessments are summarized together).

- PK variables were limited to concentrations of macitentan and its metabolite.
- Rules for reassignment to time window have been updated to include variables with assessments not every 12 weeks (Tables 7 to 11 have been added).
- It has been specified that imputation of macitentan start date is only done if there is evidence of treatment (if at least an incomplete end date for macitentan is present)
- Imputation rules for study concomitant end date has been updated to account for different scenarios. Imputation rule for PAH diagnosis date has been modified to account for subjects < 2 y.o.
- Clarifications have been added throughout the document.

Version 3.0

This Statistical Analysis Plan was amended after the release of Protocol version 9 dated 23 November 2021.

- The planned statistical analyses have been modified to account for the changes in study design, reordering of endpoints and addition of a cohort of children < 2 years old in the new version of the protocol (V9).
  - The study design has been amended from an event-driven study to a calendar driven study.
  - Updates to terminology and visits have been incorporated:
    - Study period changed to Core Period
    - Added End of Core Period Visit
    - Added Single Arm Extension Period (to be addressed in a separate SAP(s)).
  - Three analysis timepoints have been added:
    - Analysis 1 of the Core Period,
    - Analysis 2 of the Core Period, and
    - Analysis 3 final analyses performed at the end of the single-arm extension period.
    - This SAP focuses on the Core Period Analysis only (Analysis 1 and Analysis 2). The single arm extension period and CSR analyses will be described in separate SAP(s).

  - Added cohort of children < 2 years old throughout
- Trough PK endpoint moved from secondary endpoint to primary endpoint
  - Primary PK endpoint: Trough plasma concentration at Week 12 (≥ 2 y.o.) and Week 4 (< 2 y.o.)
- CEC-confirmed disease progression moved from primary efficacy endpoint to secondary efficacy endpoint
- Selected exploratory endpoints moved to secondary efficacy endpoints. In addition, the endpoints were updated to specify the key timepoint of assessment:
  - Proportion of subjects with WHO FC I or II (yes/no) at Week 24
  - Percent of baseline plasma NT-proBNP at Week 24
  - Change from baseline in mean daily time spent in moderate to vigorous activity measured by Accelerometry at Week 48
  - Change from baseline in Echocardiography variables BSA-normalized TAPSE and left ventricular eccentricity index) at Week 24
  - Change from baseline in QoL as measured by the PedsQLTM Generic Core Scales Short Form (SF15) at Week 24
- Remaining exploratory endpoints updated to specify the key timepoint of assessment.
- Analysis Sets updated
  - The Per Protocol Analysis Set was dropped as an analysis set due to the efficacy endpoint, time to CEC-confirmed disease progression, is now a secondary endpoint.
  - PK Analysis Sets updated for different age cohorts (< 2 y.o., ≥ 2 y.o.) and to reflect primary analysis set
  - Full Analysis Set updated for different age cohorts (< 2 y.o., ≥ 2 y.o.)
  - Safety Analysis Set updated for different age cohorts (< 2 y.o., ≥ 2 y.o.)
- Statistical Analyses have been removed from the analysis plan as the primary endpoint has shifted. The following analyses have been removed for the time to CEC-confirmed Disease Progression Efficacy Endpoint:
  - Group sequential boundaries to account for multiplicity of analysis looks has been dropped and p-values are compared to the nominal 0.05 2-sided alternative as this is not a formal significance conclusion. (NOTE: an alpha spending rule may be implemented in separate SAP(s)).
  - Hazard Ratio and 95% CIs using repeated CI methodology.
  - Stratified proportional hazards analysis
  - Bayesian analysis
  - Competing risk analysis
  - Exploratory analysis assessing the potential confounding effect accounting for crossovers to macitentan after CEC-confirmed disease progression in the SoC arm
  - Subgroup analyses for all except the ERA/non-ERA subgroup
- A derivation to identify miss-stratification errors for the stratification variable ERA planned/ongoing has been added since not collected in eCRF,
- All text related to activity covered in a separately maintained document have been removed so as not to create inconsistencies and the document specified:
  - IDMC Charter
  - CEC Charter
  - Firewall Charter

  - Communication Plan
  - Natural Disaster/Major Disruption/Pandemic Appendix
- COVID-19 related PDs and AEs have been updated to Natural Disaster/Major Disruption/Pandemic related PDs and AEs
- The List of Summary Tables, Listings and Figures has been dropped form the SAP as a standalone DPS document will be created to detail the List of Summary Tables, Listings and Figures and to avoid inconsistencies between this SAP and the DPS.
- Clarifications have been added throughout the document
- The document has been streamlined to focus on statistical analyses.

Version 2.0

This Statistical Analysis Plan was amended after the release of Protocol version 7 dated 16 September 2020.

- The planned statistical analyses have been modified to account for the crossover to macitentan in the Standard of Care (SoC) arm after Central Event Committee (CEC)-confirmed disease progression offered with the new version of the protocol (V7).
  - For each secondary efficacy variable, the treatment effect will be estimated by accounting for crossovers to macitentan after CEC-confirmed disease progression in the SoC arm using two statistical methods:
    - Marginal structural models with inverse probability of censoring weighting, and
    - Rank-preserving structural accelerated failure time models.
  - For the exploratory variables, only values collected up to end of randomized macitentan or SoC + 7 days or up to start of macitentan for crossover subjects will be considered for analysis.
  - For the safety variables, adverse events and laboratory data, an observation period post-crossover is added.
- The analysis of recurrent events, as well as the description of number of days hospitalized, have been deleted due to possible crossover to macitentan in the SoC arm.
- Six-minute walk distance was added as an exploratory variable.
- Clarifications have been added throughout the document.
- COVID-19-related analyses have been added.

LIST OF ABBREVIATIONS AND ACRONYMS

ADaM	Analysis Data Model
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC_{τ}	Area under the plasma concentration-time curve during one dosing interval
BCAC	Baseline Characteristics Adjudication Committee
BP	Blood pressure
BSA	Body surface area
CDISC	Clinical Data Interchange Standards Consortium
CDC	Centers for Disease Control and Prevention
CEC	Clinical Event Committee
CHD	Congenital heart disease
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRO	Contract research organization
CSR	Clinical study report
CV	Coefficient of variation
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
EOM	End-of-Macitentan
EOS	End-of-Study
EOSoC	End of Standard of Care
ERA	Endothelin receptor antagonist
FAS	Full analysis set
FC	Functional class
HIV	Human immunodeficiency virus
hPAH	Heritable pulmonary arterial hypertension
HR	Hazard Ratio

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the statistical analyses and data presentation of the PK, efficacy and safety endpoints included in the Core Period (Analysis 1 and 2) clinical study report (CSR) of the study AC-055-312. This version of the SAP is used only in countries where Protocol V9.0 is approved. Analysis 1 will be presented in an Interim CSR.

Analyses planned for the final CSR including Analysis 3 and single-arm extension period will be described in a separate SAP. Source data for the analyses will be provided as Statistical Analysis Software (SAS®) data sets according to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM). Analysis data sets will be derived as SAS® data sets according to the CDISC Analysis Data Model.

2. STUDY DESIGN AND VISIT AND ASSESSMENT SCHEDULE

2.1. Study design

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

Subjects ≥ 2 years old at Visit 2 will be randomized in a 1:1 ratio to either receive macitentan or continue standard of care (planned SoC). Randomization is stratified by ongoing/planned endothelin receptor antagonist (ERA) treatment (yes vs no) and by World Health Organization functional class (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 at most 40% of the overall number of subjects randomized.

The cohort of children < 2 years old at Visit 2 will not be randomized but will enter directly into the macitentan arm after screening. The ERA cap and the exclusion criterion related to prior/concomitant use of macitentan at Visit 2 applicable for over 2 years old do not apply to the under 2 cohort. Therefore, children < 2 years old may enter the study on macitentan. Additionally, oral/inhaled prostanoids are allowed as PAH-specific background therapy for 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. Overall, 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 analysis including the core and the single-arm extension periods).

This SAP describes the statistical analyses for Analysis 1 and Analysis 2.

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) for subjects ≥ 2 y.o. For the cohort of children < 2 y.o. the screening period ends with their enrollment date (Day 1 - Visit 2), or screening failure.

Core Period: Commences with randomization date for subjects ≥ 2 y.o. and with Visit 2 start date for subjects < 2 y.o. and continues until the End-of-Core Period (EOCP) visit end date.

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

Post-Event Study Phase (Post-Event SP): Begins the day after the first CEC-confirmed disease progression event date and continues until EOCP visit end date. During Post-Event SP pulmonary arterial hypertension (PAH)- specific background treatment may be escalated in both treatment arms as per local practice. Any additional treatment, including intravenous (i.v.) or subcutaneous (s.c.) 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's judgement.

End-of-Macitentan (EOM): All subjects treated with macitentan who prematurely discontinue macitentan within the Core Period (prior to EOCP visit end date) 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 the Core Period. Survival data will be collected at least yearly after the last regular Core Period study visit and until the EOCP. In these subjects the last survival follow-up contact constitutes their EOCP/EOS.

End-of-Core Period (EOCP): This visit will be the last visit before the clinical cutoff date for Analysis 2. The cutoff date for Analysis 2 is set to occur in the first quarter of 2024 and will be announced by the sponsor. All subjects will have their EOCP visit performed prior to this cutoff date. For subjects ongoing in the core period and for subjects prematurely discontinuing study visits but continuing in the study for survival follow-up visits, the cutoff date will be the EOCP. For subjects who died, the date of death will be the EOCP. For subjects prematurely discontinuing the study, the EOS date will be the EOCP, defined as in Section 9.1.1.

Safety Follow-up Period: Applies to subjects who prematurely discontinue macitentan or SoC treatment during the Core Period. It begins immediately after premature end of treatment and ends at least 30 days after EOCP 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 EOCP.

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

2.1.1. PK Assessments

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

For up to 40 subjects ≥ 2 y.o. receiving macitentan (randomized or cross-over) a PK profile will be collected as part of a PK substudy at Visit 3; the PK samples will be collected at pre-dose and 1h, 2h, 4h, 8h, 12h and 24h post-dose. Provision of full PK profile is optional for participants.

For subjects < 2 y.o., trough samples (i.e., pre-dose) will be drawn on Weeks 4 and 8.

For subjects < 2 y.o. sparse samples will be collected after the first macitentan dose at Visit 2 (2h, 5h and 24h post-dose).

PK trough data (for all subjects) and PK profiles (for subjects ≥ 2 y.o.) will be presented in the CSR and the analyses are explained in this SAP.

PK modeling and sparse samples (for subjects < 2 y.o.) will be reported separately (i.e., not included in the CSR).

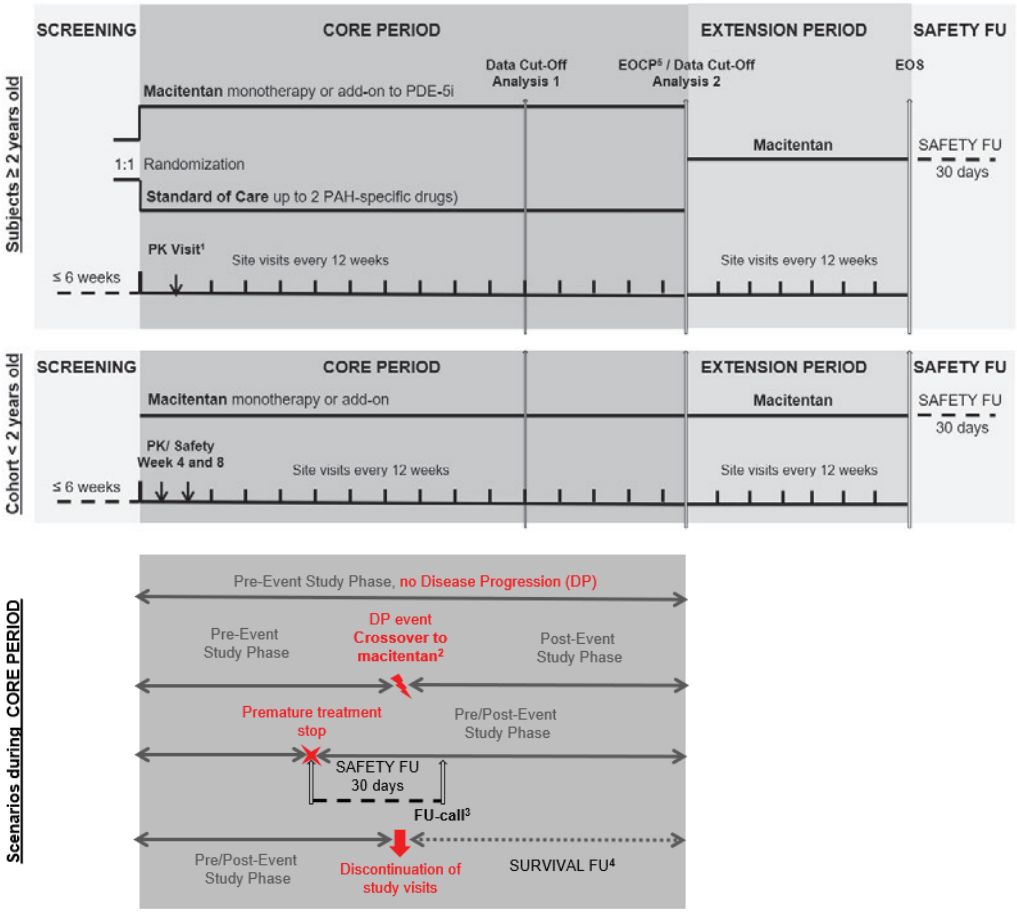
2.1.2. Study Duration

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

This is 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. The single arm extension period will start after the cutoff date for Analysis 2. Subjects may continue into the single arm extension period following EOCP.

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 Protocol 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.

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. 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.

2.1.3. Study Committees

An IDMC will review efficacy, safety and tolerability data at regular intervals according to the IDMC charter. The IDMC responsibilities are detailed in the IDMC Charter.

An Independent Statistical Analysis Center (ISAC) (not otherwise involved with study conduct or statistical analysis) will have exclusive access to the randomization list and will support the IDMC for their review and recommendation over the entire course of the study.

A Clinical Event Committee (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. The CEC process is defined in the CEC charter.

An independent Baseline Characteristics Adjudication Committee (BCAC) will review and approve the enrollment of subjects with PAH with co-incidental congenital heart disease (CHD) i.e., small atrial septal defect, ventricular septal defect or patent ductus arteriosus which themselves do not account for the development of elevated pulmonary vascular resistance (PVR). This independent review is governed by a Charter.

An Independent Liver Safety Data Review Board, a non-study specific external expert committee of hepatologists, will receive cases of serious hepatic events of special interest from the sponsor, as described in the "Enhanced Pharmacovigilance plan". This board provides ongoing assessment and advice regarding cases that may require further evaluation during the study.

2.2. Primary objective(s)

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

2.2.1. Measures to minimize the bias

In order to minimize the assessment bias inherent to the open-label design, a Firewall Charter and Communication Plan have been put into place that fully describes blinded and unblinded roles and procedures for study team members as well as clinical research organization (CRO) partners. In addition, the following measures reduce the bias during review of endpoints:

- Disease progression endpoints are adjudicated by the CEC which is blinded to study treatment
- Echo parameters are read by central echo readers who are blinded to study treatment.

No strategic decision on this SAP was made by unblinded team members.

The randomization list will be stored by the secure data office and will be shared with the CRO and with the sponsor's biostatistics department only after Analysis 1 timepoint, at which point the entire study team will be unblinded

2.3. Visit and assessment schedule

The visit and assessment tables are shown in Table 2 (Core Period for subjects ≥ 2 y.o.), and Table 3 (Core Period for subjects < 2 y.o.) below.

Table 2: 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	-
Subject narrative		-	X	-	-	X	-	-	-	-	-	-
Supportive data for DP[7]		-	-	-	-	X	-	-	-	-	-	-
NT-proBNP sampling		-	X	-	X	X	X[8]	-	X	-	X	-
Echocardiography		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	-

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]
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	-	-	-	-	-	-	-
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 3: 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	-	-	-	-	-
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	-

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]
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 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.

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.

3. OBJECTIVES

3.1. Primary objective(s)

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

3.2. Secondary objectives

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

4. CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1. Changes to the analyses planned in the study protocol

1. Spider plots for QoL are listed in the protocol version 9 but not included in this document. This change from protocol is due to the differences between components of the questionnaire between age groups, making it difficult to let them be summarized in the same graph. Box plots of total scores of QoL PedsQL SF-15 are considered sufficient, and spider plot presentation of the data by domain (i.e., physical, emotional, social and school functioning) will not add any meaningful information.

2. Box Plots for components of PedsQL for English-speaking US subjects (Heart problems and treatment, General fatigue) are listed in the protocol version 9 but not included in this document. This change from protocol is due to a very small sample size randomized in US.

3. Demographics and Baseline Characteristics will be presented overall and by age, sex and race. The subgroups WHO FC, PDE5-I at baseline, ERA ongoing/planned at baseline, PAH etiology and region will not be presented given the reduced sample size and that the study is not powered to demonstrate efficacy. Those subgroups will, however, still be analyzed for the time to event endpoints. Additionally, subgroup analyses for Adverse Events by age, sex and race have been added for a deeper understanding of the distribution of AE within each of these categories.

4. Kaplan Meier estimates (tables and graphs) will not be presented for AE of special interest and marked abnormal laboratory values given the reduced sample size .

5. The exploratory endpoint “6-minute walk distance at Weeks 12, 24 and 48” will not be presented for Analysis 1 given the small sample expected to provide data (endpoint was introduced in protocol V8 [25-Jan-21] and only patients aged 6 years and older and developmentally capable to perform the test can provide data. These endpoints will be presented at Analysis 2.

6. Scatter plots for worst post-Baseline values versus Baseline for laboratory data will not be produced as well as eDISH plots. Listings suffice.

4.2. Changes in the conduct of the study / data collection

Section 6.5 of Protocol mentions palatability and acceptability endpoints for subjects randomized to macitentan only, but the collection of these endpoints was performed also for subjects < 2 y.o. who are on macitentan, and consequently summarized for them too.

4.3. Clarification concerning endpoint definitions and related variables or statistical methods

Study periods:

- It has been clarified that Pre- and Post-Event SP respectively ends and starts with the **first** CEC-confirmed disease progression event (i.e., pre-event study phase ends with date of first CEC-confirmed disease progression event, and post-event SP starts the day after date of first CEC-confirmed disease progression event).

Secondary efficacy variables:

- For the analysis of the secondary efficacy variables of time to first CEC-confirmed disease progression, time to hospitalization due to PAH, and time to death (all causes), reporting of fatal events need to be cross checked with the Event Adjudication System (EAS) form (e.g., not all events will have a DP form in the eCRF).
- For the analysis of the secondary efficacy variable time to first CEC-confirmed hospitalization for PAH, subjects who have died without any CEC-confirmed hospitalization for PAH having been reported will be considered for the analysis as having a CEC-confirmed hospitalization for PAH at the time of death. This clarification is made to eliminate the informative censoring at the time of death.
- Exploratory p-values will always be shown, clarifying in a footnote that no formal hypothesis testing is done

Exploratory variables:

- It has been clarified that for crossover subjects, exploratory endpoints are analyzed up to start of macitentan or end of SoC + 7 days, whichever comes first, as the start of macitentan could be earlier than end of SoC + 7 days.
- Exploratory p-values will always be shown, clarifying in a footnote that no formal hypothesis testing is done

Safety variables:

- The definition of start of SoC has been clarified in the SAP and is considered to be equal to the randomization date. This has been done to minimize the selection bias induced by the heterogeneity of the SoC composition (e.g., ongoing non-PAH-specific therapies) and the difficulty to capture a valid first intake date. As a consequence of this definition, all subjects randomized to SoC will be included in the Safety Set, regardless of exposure to SoC.
- It has been clarified that for the analyses in the 'Overall core period', safety endpoints are analyzed for crossover subjects only up to start of macitentan or end of SoC + 30 days, whichever comes first, as the start of macitentan could be earlier than end of SoC + 30 days.

- Adverse events of special interest have been defined based on the macitentan AESI definition guidance with input from the trial safety lead.
- The safety analysis set has been split into two analyses sets for each cohort (< 2 y.o. and ≥ 2 y.o.).

Other variables:

- In order to assess the potential impact on the efficacy analyses, which is performed, as per intent-to-treat principle, by considering the stratification factor values entered in IRT, a concordance contingency table crossing the stratification factors values entered in IRT versus the values documented in eCRF (WHO FC) or gathered from PDs (ERA treatment ongoing/planned) will be provided.
- The analyses of demographics, baseline, follow-up duration and disposition variables are not described in the section 11 of the clinical study protocol and are therefore defined in this SAP.
- In Protocol previous or concomitant therapies are defined referring to date of Informed Consent while in this SAP they have been defined using the randomization date, considering it as more meaningful timepoint.

Graphical representation:

- Overall, graphical representations were added to depict variables profiles over time by treatment group.

5. DEFINITION OF VARIABLES

This section provides the definitions for all variables used in the analyses.

5.1. Subject disposition

The subject disposition table will include the following variables:

Applicable to all subjects (both ≥ 2 years old and < 2 years old):

- Subjects screened (subjects with at least one screening date);
- Subjects re-screened (subjects with at least two screening dates);
- Screen failures (screened, but not randomized);
- Subjects treated (either randomized to macitentan and who received at least one dose of macitentan or randomized to continue SoC);
- Subjects who prematurely discontinued macitentan or SoC during the Core Period;
- Subjects who prematurely withdrew from the regular study visits during the Core Period;
- Subjects who prematurely withdrew from the study during the Core Period;
- Subjects ongoing at the time of data cut, defined as subjects who did not complete the EOS visit before the data cut;

- Subjects who are lost to follow-up in the Core Period, defined as subjects who completed the EOS visit with reason of study stop ‘Lost to Follow-Up' in the eCRF page ‘End of Study’;
- Subjects who completed the Core Period;
- Subjects enrolled in single-arm extension study;
- Subjects who are lost to follow-up in the single-arm extension study;*
- Subjects who completed the study.*

*not valid for Core Period Analysis.

Applicable only for subjects ≥ 2 years old:

- Subjects randomized (randomization date and randomization number present in IRT),
- Crossover subjects (subjects randomized to SoC who received at least one dose of macitentan after CEC-confirmed disease progression) during Core Period.

Applicable only for subjects < 2 years old:

- Subjects enrolled (assigned to macitentan and with enrollment date in the IRT system).

5.2. Demographics

The demographic and baseline characteristic variables include the following:

- Sex (Female/Male),
- Age (years) as continuous variable and in categories:
  - ≥ 2 to < 6 years / ≥ 6 to < 12 years/ ≥ 12 to < 18 years, for subjects ≥ 2years,
  - < 6 months/≥ 6 months, for subjects < 2 years
- Body weight at baseline (kg),
- Height/length at baseline (cm),
- Presence of Down syndrome (Yes/No),
- Race (Black or African American / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander / Asian / White / Other / Not applicable)
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino / Unknown),
- Region (North America vs Europe/Israel vs Asia/Australia vs Other).

  Each country is assigned to a region based on the Standard Country or Area Codes for Statistical Use M49 (Section 13).

5.3. Stratification variables

The stratification variables at randomization:

- Ongoing/planned ERA (yes vs no),

- WHO FC at randomization (FC I/II vs III),

will be analyzed as entered in the IRT system by the investigator during the randomization transaction.

The concordance between IRT and the actual value of stratification variables at Visit 2 (e.g., IRT miss-stratification errors) are identified by:

- Subjects with miss-stratification of ongoing/planned ERA will be assessed and documented as a PD. Concordance between IRT and actual treatment regimen will be confirmed by the absence of the specific 'miss-stratification' PD,
- Subjects with miss-stratification of WHO FC will be assessed using the value from Visit 2 eCRF.

The stratification variables do not apply to the cohort of subjects < 2 years old.

5.4. Baseline disease characteristics

The baseline disease characteristic variables are defined as follows:

- PAH etiology:
  - Idiopathic pulmonary arterial hypertension (iPAH),
  - Heritable pulmonary arterial hypertension (hPAH),
  - PAH associated with HIV,
  - Drug- or toxin-induced PAH,
  - PAH with co-incidental CHD,
  - PAH associated with CHD post-operative:
    - Post-operative PAH,
  - PAH associated with connective tissue disease (PAH-aCTD),
- Time from PAH diagnosis in days, defined as the time from PAH diagnosis to randomization,
- Right heart catheterization (RHC; Yes/No),

  If yes:
  - Time from RHC in days, defined as the time from RHC date to randomization,
  - Mean pulmonary arterial pressure (mPAP; mmHg),
  - Pulmonary artery wedge pressure (PAWP; mmHg),
  - Pulmonary vascular resistance index (PVRi; Wood Unit $\times$ m^2),
- Total number of signs and symptoms of PAH
- Signs and symptoms of PAH:
  - Dyspnea with exertion (Yes/No),

  - Dyspnea at rest (Yes/No),
  - Cyanosis with exertion (Yes/No),
  - Cyanosis at rest (Yes/No),
  - Hemoptysis (Yes/No),
  - Chest pain/discomfort (Yes/No),
  - Near-syncope/dizziness (Yes/No),
  - Syncope (Yes/No),
  - Fatigue (Yes/No),
  - Hepato-jugular reflux (Yes/No),
  - Hepatomegaly (Yes/No),
  - Peripheral edema (Yes/No),
  - Ascites (Yes/No),
  - General edema (Yes/No),
  - S3 gallop (Yes/No),
- WHO FC (I / II / III / IV) as per CRF,
- Panama FC (I / II / IIIa / IIIb / IV),
- Ongoing/planned ERA treatment at randomization as per IRT stratification factor (Section 5.3) (Yes/No),
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at baseline (pmol/L),
- Baseline BSA-normalized TAPSE (mm/m^2), as per central review of Echocardiography,
- Baseline left ventricular eccentricity index, as per central review of Echocardiography,
- Planned/ongoing SoC at randomization as per IRT questions:
  - Non PAH-specific therapies,
  - PDE-5 inhibitor (PDE-5i) monotherapy,
  - ERA monotherapy,
  - Inhaled/oral prostanoids monotherapy,
  - Soluble guanylate cyclase (sGC) stimulator monotherapy,
  - PDE-5i + ERA,
  - PDE-5i + inhaled/oral prostanoids,
  - ERA + inhaled/oral prostanoids,
  - ERA + sGC stimulator,
  - Inhaled/oral prostanoids + sGC.

In case of contradictory information among IRT questions (e.g. Non PAH-specific therapies versus planned PAH treatment) the first question is disregarded.

Any other additional combination therapy not listed above (e.g. not allowed) but collected will be also displayed.

5.5. Other baseline characteristics

Quality of life at baseline:

- PedsQL™ 4.0 SF15 Short Form Generic Core Scales (all subjects):

  Total scores across all ages and by age groups, separately for parent/caregiver reports and for subject reports
- Heart Problems and Treatment Component of the PedsQL™ 3.0 Cardiac Module (English-speaking US subjects):

  Total scores across all ages, separately for parent/caregiver reports and for subject reports
- General Fatigue Component of the PedsQL™ Multidimensional Fatigue Scale (English-speaking US subjects):

  Total scores across all ages, separately for parent/caregiver reports and for subject reports

For toddlers (2 to 4 years of age), a parent or caregiver completes the QoL questionnaire and rates each item using a 5-point Likert scale per item.

For young children (5 to 7 years of age) 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 per 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.

If the subject changes age group during the conduct of the study, the same questionnaire as at Visit 2 will be continued.

The total scores are derived as per the Pediatric Quality of Life Inventory™ PedsQL™ Scoring Manual. As the answers to each question are reverse scored a higher score indicates better health.

For the cohort of subjects < 2 years old, the QoL questionnaires are not available.

Physical activity (assessed by accelerometry) at baseline:

- Mean number of hours of daytime activity
  derived as Mean of Total Wear Time (minutes)/60
- Mean count per minute of daily activity
  derived as Mean of Total Activity Counts Y-Axis/Total Wear Time (minutes)
- Mean daily time (minutes) spent in light physical activity (based on a threshold from 800 to 3199 (limits included) activity counts per minute)
- Mean daily time (minutes) spent in moderate to vigorous physical activity (based on a threshold of ≥ 3200 activity counts per minute).

The variables used for the derivations are the ones excluding epochs when the device was not worn.

Only days where at least 7 hours of data are recorded are considered for the physical activity derivations.

Note: QoL and physical activity are not collected for the cohort of subjects < 2 y.o.

5.6. Medical history

Subject medical history pertains to any previous and/or ongoing disease/diagnosis as collected during the screening visit. The original terms used by the investigators to describe diseases/diagnoses are assigned preferred terms (PTs) for classification and tabulation using the latest implemented MedDRA version dictionary.

5.6.1. Specific medical history

The specific medical history variable is the Down Syndrome (present/absent) as recorded during the screening visit and is only included in the demographics.

5.7. Previous and concomitant therapies

The original terms used by the investigators to describe therapies are assigned PTs for classification and tabulation using the latest version of the WHO Drug code and Anatomic Therapeutic Chemical (ATC Level 4) class code dictionaries.

Start and end dates that are incomplete or missing are handled according to the rules in Section 12.2.

5.7.1. Previous therapies

Previous therapies are defined as any therapy collected in the eCRF page 'Previous/Concomitant medication' for which the end date is on or prior to the date of randomization.

If the end date is missing and the start date is prior to the date of randomization, then the therapy is considered as previous if it is ticked 'Ongoing at time of randomization?= **No**' by the investigator in the eCRF.

5.7.2. Study-drug concomitant therapies

Study-drug concomitant therapies are defined based on three different periods for subjects ≥ 2 y.o.

Study-drug concomitant therapies in the *"Overall core period"* are defined as any medication/therapy collected in the eCRF page 'Previous/Concomitant medication' with:

- 'Ongoing at time of randomization = **Yes**',

  or

- start date < randomization date and (end date ≥ randomization date or missing),

  or

- randomization date ≤ start date.

Study-drug concomitant during the *"Main treatment period"* are defined as any medication/therapy collected in the eCRF page 'Previous/Concomitant medication' with:

- 'Ongoing at time of randomization = **Yes**',

  or

- start date < randomization date and (end date ≥ randomization date or missing),

  or

- randomization date ≤ start date ≤ end of randomized macitentan or SoC.

"Post-crossover to macitentan period" study-drug concomitant are defined as any medication/therapy collected in the eCRF page 'Previous/Concomitant medication' with:

- start date < macitentan start date for subjects who cross-over and (end date ≥ macitentan start date for subjects who cross-over or missing),

  or

- macitentan start date for subjects who cross-over ≤ start date.

Study-drug concomitant therapies are defined based on two different periods for subjects < 2 y.o.

Study-drug concomitant therapies in the *"Overall core period"* are defined as any medication/therapy collected in the eCRF page 'Previous/Concomitant medication' with:

- 'Ongoing at time of randomization = **Yes**',

or

- start date < macitentan start date and (end date ≥ macitentan start date or missing),

or

- macitentan start date ≤ start date.

Study-drug concomitant during the *"Main treatment period"* are defined as any medication/therapy collected in the eCRF page 'Previous/Concomitant medication' with:

- 'Ongoing at time of randomization = **Yes**',

or

- start date < macitentan start date and (end date ≥ macitentan start date or missing),

or

- macitentan start date ≤ start date ≤ end of macitentan.

Study-drug concomitant therapies for COVID-19 infection are defined as any study-drug concomitant therapies with indication as COVID-19 coded term.

5.7.3. PAH-specific concomitant therapies

PAH-specific concomitant therapies are defined as any medication/therapy collected in the eCRF page 'PAH-Specific Treatment', fulfilling the same criteria described in section 5.7.2.

5.8. Other subject characteristics

For females of childbearing potential, use of hormonal contraceptives will be collected in the eCRF.

The original terms used to describe contraceptives will be coded using preferred terms from the most recent version of the WHO Drug dictionary and analyzed with the study-drug concomitant therapies.

5.9. Study treatment exposure and compliance

5.9.1. Duration of randomized treatment

For subjects ≥ 2 years old, duration (weeks) of randomized treatment (macitentan or SoC) during the core period, is defined as the time elapsing between the date of first study drug intake and the date of last intake of randomized study drug + 1 (in days) / 7, regardless of any treatment interruptions.

5.9.2. Duration of treatment with macitentan

For all subjects, duration of macitentan treatment during the Core Period is defined as the time elapsing between the date of start of macitentan and the end of macitentan + 1 (in days) / 7 or end of the Core Period, whichever occurs first.

5.9.3. Drug accountability and compliance with macitentan

This paragraph is only applicable to macitentan (administered as randomized treatment [subjects ≥ 2 years old], administered as treatment [subjects < 2 years old], or initiated at crossover) as it is the only study drug prescribed in this study with a formal targeted dose and compliance. Conversely, the SoC is administered at the discretion of investigator per local practice with no common posology/constitution.

The reasons of non-compliance are the following ones:

- Blister not returned,
- Treatment interrupted due to AE,
- Intake error / Treatment dispensation error,
- Natural disaster/Major disruption/Pandemic-related (recorded as "Treatment interrupted due to AE" and corresponding AE is reported with Natural disaster/Major disruption/Pandemic coded term),
- Other.

5.9.4. Macitentan discontinuation

A premature permanent macitentan discontinuation is defined as stopping macitentan (randomized treatment, enrolled treatment or crossover treatment) prior to the EOCP visit. Subjects discontinuing early are identified by having a macitentan discontinuation date and/or a reason entered on the 'Premature Discontinuation of Macitentan Study Treatment' eCRF page.

Reasons for premature treatment discontinuation are as follows:

- Death,
- Lost to follow-up,
- Pre-specified study treatment discontinuation criteria,
- Parent/Subject decision (further split into: Tolerability related, Efficacy related, Other, Not known),
- Physician decision (further split into: Adverse event, Lack of efficacy / Treatment failure, Other),
- Sponsor decision (further split into: Study terminated, Other),
- Natural disaster/Major disruption/Pandemic-related (recorded as "Physician decision: AE" and corresponding AE is reported with Natural disaster/Major disruption/Pandemic coded term).

An additional category will be derived as 'No reason provided' for subjects where the reason is missing.

5.9.5. SoC discontinuation

SoC discontinuation is reached if a planned PAH-specific drug class is discontinued, or if any additional PAH-specific drug class is added prior to the EOCP visit.

Subjects discontinuing early are identified by having a SoC discontinuation date and/or a reason entered on the 'Premature Discontinuation of SoC' eCRF page.

Reasons for premature treatment discontinuation are as follows:

- Death,
- Lost to follow-up,
- Pre-specified study treatment discontinuation criteria,
- Parent/Subject decision (further split into: Tolerability related, Efficacy related, Other, Not known),
- Physician decision (further split into: Adverse event, Lack of efficacy / Treatment failure, Other),
- Sponsor decision (further split into: Study terminated, Other),
- Natural disaster/Major disruption/Pandemic-related (recorded as "Physician decision: AE" and corresponding AE is reported with Natural disaster/Major disruption/Pandemic-related coded term).

An additional category will be derived as 'No reason provided' for subjects where the reason is missing.

5.10. Duration of follow-up

5.10.1. Duration of time on regular visits

Duration on regular visits (weeks) is defined as the time elapsing between date of randomization (or Visit 2 for subjects < 2y.o.) and the date of last scheduled visit performed + 1 (in days) / 7.

5.10.2. Premature study visit discontinuation

Premature study visit discontinuations along with date and reason are collected in a dedicated page. Visit discontinuations due to natural disaster, major disruption or pandemic are identified with specific prefix in the reason for study visit discontinuation in the eCRF.

5.10.3. Duration of time on study

Duration on study (weeks) is defined as the time elapsing between date of randomization (or Visit 2 for subjects <2y.o.) and the date of EOCP visit + 1 (in days) / 7.

For subjects who have prematurely discontinued regular study visits, the last survival follow-up contact will be used as the EOCP.

For subjects who have prematurely discontinued the study, the last visit performed will be used as the EOCP.

5.11. Study withdrawal

A premature withdrawal of study happens when parent(s) / legally designated representative (or the study participant) withdraws the consent to continue the study according to the original schedule of assessments and at the same time prohibit any further data collection or if the subject is lost to follow-up. Subjects discontinuing early are identified by having a study discontinuation date and a reason entered on the corresponding eCRF page.

Possible reasons for early study withdrawal are as follows:

- Death,
- Lost to follow-up,
- Parent/Subject decision (further split into: Withdrawal of consent, Tolerability related, Efficacy related, Other),
- Physician decision (further split into: Adverse event, Other),
- Sponsor decision (further split into: Study terminated, Other),
- Natural disaster/Major disruption/Pandemic-related (recorded as "Physician decision: AE" and corresponding AE is reported with Natural disaster/Major disruption/Pandemic-related coded term).

An additional category will be derived as 'No reason provided' for cases where the reason is missing.

5.12. Efficacy variables

5.12.1. Secondary efficacy variables

5.12.1.1. 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 have not experienced any CEC-confirmed disease progression before the EOCP will 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 have discontinued prematurely regular study visits, the last survival follow-up contact will be used as the EOCP visit.

Time to first CEC-confirmed disease progression will be 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.) + 1 or, for censored subjects, as censoring date minus date of randomization (or Visit 2 for subjects < 2 y.o.) + 1.

The events to be considered for the first CEC-confirmed disease progression are:

- 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 i.v. 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.

In case of concomitant events happening on the same day, the first one in hierarchical order will be summarized, where the hierarchical order is set in the same manner of the above list.

Note: As per CEC Charter Section 11 a list of pre-identified events will be submitted to the CEC for adjudication irrespective of whether the event was reported on the eCRF DP page (e.g., SAEs with fatal outcome). These events can be identified on the EAS CRF page.

5.12.1.2. 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 and irrespective of previous Clinical Worsening confirmed by the CEC.

Subjects who have died without any CEC-confirmed hospitalization for PAH having been reported will be considered for the analysis as having a CEC-confirmed hospitalization for PAH at the time of death.

Subjects who have not experienced any CEC-confirmed hospitalization for PAH or death before the end of the core period, will have their time to first hospitalization right-censored at the time of EOCP visit or cutoff date for the respective analysis, whichever occurs first. For subjects who have

discontinued prematurely regular study visits, the last regular study visit performed will be used as the EOCP based on the fact that any events occurring later to this date will not be adjudicated. Time from randomization to first CEC-confirmed hospitalization will be 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.) +1 or, for censored subjects, as censoring date minus date of randomization (or Visit 2 for subjects < 2 y.o.) +1.

5.12.1.3. 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 still alive at EOCP or who have died due to reasons other than PAH (CEC-confirmed) before the end of the core period, will have their time to death right-censored at the time of EOCP visit/death or cutoff date for the respective analysis, whichever occurs first. For subjects who have discontinued prematurely regular study visits during the core period, the last survival follow-up contact will be used as the EOCP.

Time from randomization to CEC-confirmed death due to PAH will be expressed in days and calculated as the onset date of the CEC-confirmed death for PAH minus date of randomization+1 or, for censored subjects, as censoring date minus date of randomization+1.

5.12.1.4. Time to death (all causes)

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 still alive at the data cut-off date for each analysis will have their time to death right-censored at the time of EOCP or cut-off date for the respective analysis, whichever occurs first. For subjects who have discontinued prematurely regular study visits during the core period), the last survival follow-up contact will be used as the EOCP.

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

Note: As per CEC Charter Section 11 a list of pre-identified events will be submitted to the CEC for adjudication irrespective of whether the event was reported on the eCRF DP page (e.g., SAEs with fatal outcome). These events can be identified on the EAS CRF page.

5.12.1.5. WHO FC I or II (yes/no) at Weeks 12, 24

WHO FC will be categorized as I/II versus III/IV at 12 and 24 weeks for the main inference. WHO FC will also be categorized at every timepoint of assessment. The proportion of subjects with WHO FC equal to I or II will be provided for every timepoint of assessment out of the total number of subjects with available data (i.e., those having a reported value of I through IV: proportion WHO FC I/II = number WHO FC I + II / number WHO FC I + II + III + IV) and only considering values

collected up to end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects.

For subjects < 2 y.o. who enter the macitentan arm without randomization, values collected until end of core period or end of macitentan treatment + 7 days (whichever is earlier) are considered.

All recorded scheduled assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Section 11).

5.12.1.6. Percent of baseline in plasma NT-proBNP (pmol/L) at Weeks 12, 24

The percent of baseline at Week 12 and at Week 24 in plasma NT-proBNP, defined as 100* (NT-proBNP at timepoint / NT-proBNP at baseline) will be calculated. The percent of baseline in plasma NT proBNP will also be calculated at every timepoint of assessment up to end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects.

For subjects < 2 y.o. who enter macitentan arm without randomization, values collected until the end of the core period or end of macitentan treatment + 7 days (whichever is earlier) are considered. The absolute change from baseline at Week 12 and at Week 24 in plasma NT-proBNP, defined as the difference between NT-proBNP at timepoint - NT-proBNP at baseline will also be calculated.

All recorded scheduled assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Section 11).

5.12.1.7. Mean daily time spent in moderate to vigorous physical activity as measured by accelerometry at Week 48

The change from baseline to Week 48 in mean daily time (minutes) spent in moderate to vigorous physical activity, based on a threshold ≥ 3200 activity counts per minute, is the secondary endpoint based on accelerometry.

However, 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, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects, for subjects ≥ 2 y.o.

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).

Accelerometry variables are not collected in the cohort of subjects < 2 years old.

5.12.1.8. Echocardiography variables at Week 24

The echocardiographic variables of interest are:

- BSA-normalized TAPSE, expressed as change from Baseline to Week 24.

  BSA (m^2) is calculated as $0.007184 \times weight^{0.425} \times height^{0.725}$, with weight expressed in kg and height in cm.

  For each visit the BSA-normalized TAPSE (mm/m^2) is TAPSE assessed at the visit divided by the corresponding BSA (derived at the same visit).

- Diastolic Left Ventricular Eccentricity Index (Diastolic LVEI) and Systolic Left Ventricular Eccentricity Index (Systolic LVEI), 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, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects. For subjects < 2 y.o. who enter macitentan arm without randomization, values collected until end of core period or end of macitentan treatment + 7 days (whichever is earlier) are considered.

All recorded scheduled assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (seeTable 8: Time windows for reassignment of physical activity and 6MWT).

5.12.1.9. Quality of life as measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15) at Week 24

The main QoL variables of interest are the total scores as measured by the PedsQL™ 40 Generic Core Scales Short Form (SF15) across all ages and by age groups, separately for parent/caregiver reports and for subject reports and expressed as change from Baseline to Week 24.

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 for subjects ≥ 2 years old or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects.

The total scores are derived as per the Pediatric Quality of Life Inventory™ PedsQL™ Scoring Manual. As the answers to each question are reverse scored a higher score indicates better health.

All recorded scheduled assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (seeTable 10).

Quality of life is not collected in the cohort of subjects < 2 y.o.

Additional quality of life variables are defined in Section 5.14.

5.12.2. Exploratory efficacy variables

5.12.2.1. Panama FC I or II (yes/no) at Week 24

Panama FC will be categorized as I/II versus IIIa/IIIb/IV at Week 24. The Panama FC values are 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: proportion Panama FC I/II = number Panama FC I + II/ number Panama FC I + II + IIIa + IIIb + IV) and only considering values collected up to end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects.

For subjects < 2 y.o. who enter macitentan arm without randomization, values collected until end of core period or end of macitentan treatment + 7 days (whichever is earlier) are considered.

All recorded scheduled assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Section 11).

The Panama FC is tailored for children up to 16 years of age and thus its assessment will discontinue in children > 16 years of age.

5.12.2.2. Additional Physical activity (accelerometry) at Weeks 12, 24 and 48

The additional accelerometry variables of interest are:

- Mean number of hours of daytime activity,
- Mean count per minute of daily activity,
- Mean daily time (minutes) spent in light physical activity based on a threshold from 800 to 3199 activity counts per minute

as defined in section 5.5. and expressed as change from Baseline to Weeks 12, 24, and 48.

Only values collected up to end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects are considered.

5.12.2.3. Six-minute walk distance at Weeks 12, 24 and 48

The variable of interest is 6-minute walk distance (m) expressed as change from Baseline to Weeks 12, 24 and 48.

Only values up to end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects are considered.

This variable was added via a protocol amendment: only subjects randomized after protocol version 7 will have this variable available.

All recorded scheduled assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Table 8: Time windows for reassignment of physical activity and 6MWT).

Six-minute walk distance is not collected for the cohort of subjects < 2 y.o.

5.13. Safety variables

5.13.1. Adverse events

5.13.1.1. General rules for adverse events

As a general rule, the variable of interest is the occurrence of at least one AE.

If the intensity of an AE worsens between randomization date (Visit 2 for subjects < 2 y.o.) 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 worst intensity among 'mild', 'moderate' and '**severe**' during the studied period will be considered in case the same AE is reported more than once within the same subject. AEs with missing intensity will be counted as 'severe'.

5.13.1.2. Serious adverse events

An AE will be considered as serious as soon as the AE is ticked 'Serious? = **Yes'** by the investigator in the eCRF.

Otherwise, the same rules as the ones described for the AEs are applicable.

5.13.1.3. Adverse events leading to discontinuation of macitentan or SoC

All AEs with 'Action taken with macitentan or SoC = **Permanently discontinued'** will be considered as AEs leading to discontinuation of macitentan or SoC.

Otherwise, the same rules as the ones described for the AEs are applicable.

5.13.1.4. Adverse events with fatal outcome

All AEs with 'Outcome = **Death'** will be considered as AEs with fatal outcome.

5.13.1.5. Adverse events related to macitentan

Relationship to macitentan is collected only on subjects randomized to macitentan, subjects < 2 y.o. and crossover subjects. All AEs with 'Relationship = **Related'** or with missing relationship will be considered as AEs related to macitentan.

5.13.1.6. Adverse events of special interest

The adverse events of special interest are the following and are based on MedDRA version 25.1:

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

    or

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

  or

- AEs with PT containing the word “anaemia”.

- Hepatic disorders:
  - AEs with PT within “Hepatic disorders (SMQ)”, excluding the sub-SMQ “Liver-related coagulation and bleeding disturbances” and excluding PTs: “Ascites”, “Bacterascites”, “Biliary ascites” or “Haemorrhagic ascites”

- Hypotension:
  - AEs with PT equal to “Blood pressure ambulatory decreased”, “Blood pressure decreased”, “Blood pressure diastolic decreased”, “Blood pressure immeasurable”, “Blood pressure orthostatic decreased”, “Blood pressure systolic decreased”, "Blood pressure systolic inspiratory decreased", "CT hypotension complex", “Diastolic hypotension”, “Hypotension”, "Hypotensive crisis", "Neonatal hypotension", "Dialysis hypotension", “Orthostatic hypotension”, "Post procedural hypotension", “Procedural hypotension” or “Mean arterial pressure decreased”.

- Symptomatic Hypotension:
  - One AE term from the above list PLUS a term from list of MedDRA PTs, reported within 24 hours of each other: "Circulatory collapse", "Dizziness", "Dizziness postural", "Fall", "Loss of consciousness", "Presyncope", "Shock", "Shock symptom", "Syncope", "Vertigo", "Persistent postural-perceptual dizziness".

    or

  - AEs with LLT equal to "Acute hypotension", "Hypotension paroxysm", "Hypotension symptomatic", "Preshock".

- Edema and fluid retention:
  - AEs with PT within “Haemodynamic oedema, effusions and fluid overload (SMQ)”,
  - excluding any PT containing the word “site”
  - Including PT: 'Pulmonary congestion'.

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

5.13.1.7. Adverse Events of interest related to major disruption/natural disaster/pandemic

The AEs of interest related to major disruption/natural disaster/pandemic are any AE containing in “AEDECOD” anywhere in the text one of the following terms: “COVID-19”, "Coronavirus 19", "Coronavirus 19 Infection", "SAR-CoV-2", "SARS-CoV-2" or “REGIONAL CRISIS” or identified in the document "Natural Disaster_Major Disruption_Pandemic Protocol Appendix_TOMORROW (AC-055-312).docx".

5.13.2. Deaths

Death and primary cause of death are captured in a dedicated CRF form.

5.13.3. Laboratory

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

Only values collected up to end of randomized macitentan or SoC + 30 days, or up to start of macitentan or end of SoC + 30 days, whichever comes first, for crossover subjects are considered.

For subjects < 2 y.o. who enter the macitentan arm without randomization, values collected until end of macitentan treatment + 30 days are considered.

All recorded assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Table 7 Time windows for reassignment of WHO and PANAMA FCs, NT-proBNP, laboratory and vital signs).

The hematology variables are:

- Hemoglobin (g/L),
- Hematocrit (L/L),
- Erythrocyte count (10^{12}/L),
- Leukocyte count with differential counts (10^{9}/L),
- Platelet count (10^{9}/L).

The clinical chemistry variables are:

- Aspartate aminotransferase (AST; U/L),
- Alanine aminotransferase (ALT; U/L),
- Alkaline phosphatase (U/L),
- Total bilirubin (µmol/L),
- Direct bilirubin (µmol/L),
- Creatinine (µmol/L),
- Creatinine clearance (mL/min - only available for subjects randomized after protocol V7),
- Blood urea nitrogen,
- Glucose (mmol/L),
- Sodium (mmol/L),
- Potassium (mmol/L),
- Calcium (mmol/L).

All values reported as below or above the limit of quantification (e.g., '< 3', '> 100') are substituted with the limit of quantification (e.g., '< 3', is substituted by '3') for the purpose of the analysis. The values are listed including the < or > sign.

Marked Laboratory Abnormalities (MLA) are defined in Table 4 below.

Table 4: Marked Laboratory Abnormalities

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = female; M = male; ULN = upper limit of normal range.

MLA are defined as all the abnormalities fulfilling Table 4: Marked Laboratory Abnormalities criteria, that were not present at baseline. For hemoglobin (HH/HHH categories, only), marked laboratory abnormalities are those occurring after study treatment start, as it is not possible to have HH or HHH flags at baseline per definition of the abnormality.

MLA are defined based on the treatment periods (see Section 10.12).

In addition, for erythrocyte count, hemoglobin, hematocrit, AST, ALT, total bilirubin, and alkaline phosphatase the absolute values and changes from baseline over time will be considered.

5.13.4. Vital signs

For each subject the following vital signs, expressed as absolute and change from baseline will be considered:

- Diastolic blood pressure (mmHg)
- Systolic blood pressure (mmHg)
- Heart rate (beats per minute)

Only values collected up to end of randomized macitentan or SoC + 30 days, or up to start of macitentan or end of SoC + 30 days, whichever comes first, for crossover subjects are considered.

For subjects < 2 y.o. who enter the macitentan arm without randomization, values collected until end of macitentan treatment + 30 days are considered.

All recorded assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Table 7 Time windows for reassignment of WHO and PANAMA FCs, NT-proBNP, laboratory and vital signs).

5.13.5. Growth

For each subject:

- Body mass index (kg/m^2)
- Height/length (cm)
- Weight (kg)

Expressed as absolute values and change from baseline to each time point up to end of randomized macitentan or SoC + 30 days or up to start of macitentan or end of SoC + 30 days, whichever comes first, for crossover subjects, will be considered. For subjects < 2 y.o. who enter macitentan arm without randomization, up to end of macitentan + 30 days will be considered.

All recorded assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Table 7 Time windows for reassignment of WHO and PANAMA FCs, NT-proBNP, laboratory and vital signs).

The formula for calculating the BMI is:

$$BMI(kg/m^2) = \frac{\text{Weight (kg)}}{\left(\frac{\text{Height/length (cm)}}{100}\right)^2}$$

5.13.6. Sexual maturation and childbearing potential

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).

Tanner stage, expressed as absolute values at each time point up to end of randomized macitentan or SoC + 30 days or up to start of macitentan or end of SoC + 30 days, whichever comes first, for crossover subjects, will be considered.

All recorded assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Table 11: Time windows for reassignment of Tanner stage).

The childbearing potential is assessed for female subjects at each study visit (including unscheduled visits), along with sexually active status.

5.14. Quality of life variables

The QoL variables of interest are:

- the change from baseline in the total scores across ages for parent/caregiver reports and for subject reports derived for the "Heart problems and treatment" component of PedsQL™ 3.0 Cardiac Module (English-speaking US subjects)
- "General fatigue" component of PedsQL™ Multidimensional Fatigue Scale score (English-speaking US subjects)

They are derived as described in section 5.5.

Only values collected up to end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects are considered.

All recorded assessments will be assigned to the most appropriate visit timepoints according to the best fitting time-window for that assessment (see Table 10: Time windows for reassignment of QoL).

5.15. Pharmacokinetic variables

5.15.1. Primary PK variable

In subjects who are 2 years or older in the macitentan arm:

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

In subjects less than 2 years of age:

- Trough (pre-dose) plasma concentrations of macitentan and its active metabolite ACT-132577 at Week 4 (steady state conditions). If the Week 4 sample is not evaluable the Week 8 PK sample will be used.

5.15.2. Other PK variables

In subjects younger than 2 y.o. for both macitentan and its metabolite ACT-132577:

- Concentrations after the first dose of macitentan within 24 hours (2, 5, 24h post-dose) by age.

Additional PK variables will be derived and reported separately.

5.16. 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.

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. For subjects who are developmentally not capable of reporting palatability and acceptability (e.g., Down Syndrome), the caregiver will complete the questionnaire. The investigator judges whether a subject is capable completing the palatability and acceptability questionnaire.

6. DEFINITION OF PROTOCOL DEVIATIONS

The description and categorization (major and minor) of each PD, as described in the PD code list, is reported in the SDTM.

The full list of protocol deviations is in the “TOMMOROW_Study_Deviation_Rules_Document”.

Refer to the "Natural Disaster_Major Disruption_Pandemic Protocol Appendix_TOMORROW (AC-055-312).docx" for additional information on Protocol Deviations related to Natural Disaster, Major Disruption or Pandemic.

Subjects with PDs which might affect the primary PK analysis will be identified before the Analysis 1 date.

7. ANALYSIS SETS

7.1. Screened Analysis Set

The Screened Analysis Set (SCR) includes all subjects who are screened and have a subject identification number.

7.2. Full Analysis Sets

The Full Analysis Set 1 (FAS1) includes all subjects randomized to a study treatment arm via IRT (all randomized subjects ≥ 2 y.o. at Visit 2). In order to adhere to the intention-to-treat principle as much as possible for efficacy analyses:

- Subjects are evaluated according to the study treatment they have been randomized to via IRT (which may be different from the study treatment they have actually received),
- All available data from subjects at sites where Protocol V9 is effective at time of the analysis are taken into account.

Subjects will be evaluated according to stratum information used for randomization, as recorded in the IRT system (which may be different from the information available on the eCRF after data validation).

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).

7.3. Safety Analysis Sets

The Safety Analysis Set 1 (SAS1) includes all subjects ≥ 2 y.o. who received at least one dose of randomized macitentan or who were randomized to continue SoC. Subjects will be analyzed based on actual treatment received.

The Safety Analysis Set 2 (SAS2) includes all subjects < 2 y.o. who received at least one dose of macitentan.

The Safety Analysis Set 3 (SAS3) includes all subjects in the SAS1 and all subjects in the SAS2 (all subjects who received at least one dose of macitentan, either randomized or not, or who were randomized to continue SoC).

7.4. Pharmacokinetic Analysis Sets

The PK Set 1 includes all subjects ≥ 2 y.o 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. This analysis set will not be part of the report generated by this CSR SAP, but it will be described in a separate document.

The PK Set 3 includes all subjects < 2 y.o. who were 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.

The full list of protocol deviations excluding from the PK Sets 1, 2 and 3 is in the "TOMMOROW_Study_Deviation_Rules_Document".

7.5. Usage of analysis sets

The PK Set 1 (≥ 2 y.o) and PK Set 3 (< 2 y.o) will be used for macitentan and ACT-132577 trough concentration analysis.

The PK Set 2 (≥ 2 y.o) will be used for PK substudy compartmental analysis (not described in this SAP).

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

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

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

The SAS1 and SAS2 are used for the analyses of the safety variables.

SAS3 is used for all listings of safety variables.

The SCR is used for the description of subject disposition.

8. DEFINITION OF SUBGROUPS

The category in **bold type** is the reference category used in the statistical analysis of these subgroups.

The following subgroups are defined:

- WHO FC at randomization (**I/II** vs III) as per IRT,
- Ongoing/planned ERA at randomization (**Yes** vs No) as per IRT stratification factor,
- Ongoing/planned PDE-5i treatment at randomization (**Yes** vs No) as per IRT question,
- PAH etiology (**[iPAH, hPAH, HIV, drug or toxin induced,]** vs. [PAH with coincidental CHD, CHD post-operative] vs [PAH-aCTD]),
- Geographical region (North America vs **Europe/Israel** vs Asia/Australia vs Other),
  - Europe/Israel is considered reference category because it is the largest region,

- Age for subjects ≥ 2 y.o. (≥ 2 to < 6 years / ≥ 6 to < 12 years / **≥ 12 to < 18 years**),
  - The oldest age group is considered reference category because it is closest to adult population,
- Age for subjects < 2 y.o. (< 6months/ **≥ 6 months**),
- Sex (**Male** vs Female)
- Race (**White** vs Black or African American vs. Asian vs. Other [includes Other, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Applicable).

9. GENERAL STATISTICAL METHODOLOGY

For this study, summaries will be produced if 5 or more participants will be enrolled in the analysis set which the summary has to be produced on, otherwise only listings will be provided.

Summaries and graphs will include all scheduled timepoints up to Week 48. The subsequent ones will be displayed if at least 10% of the subjects in the macitentan arm have a corresponding value.

Listings will be produced on FAS3/SAS3. Additional listings on FAS2/SAS2 may be requested ad hoc and specified in the DPS.

9.1. General definitions and derivations

9.1.1. Dates

'Screening date' is defined as the date when the subject was screened for the first time and is taken directly from the IRT system.

'Re-screening date' is defined as the date when the subject was screened for the second time and is taken directly from the IRT system.

'Randomization date' is the date when the subject was randomized to either macitentan or SoC and is taken directly from the IRT system for subjects ≥ 2 y.o.

'Enrollment date' is the date when the subject is assigned to macitentan in the IRT system (for subjects < 2 y.o.).

'Visit 2 date' is the date from Visit 2 for subjects < 2 y.o.

The 'Start-of-Macitentan date' is defined as the date of the first dose of macitentan received during the study and is derived from the 'Macitentan treatment log' eCRF page.

The 'Start-of-Randomized-Treatment date / First study drug intake date' is defined as the Start-of-Macitentan date for subjects randomized to macitentan and subjects < 2 y.o. who are assigned to macitentan without randomization and is defined as the date of randomization for subjects randomized to SoC.

The 'End-of-Macitentan (EOM) date' is defined as the end date of the last dose of macitentan intake and is derived from the last interval (after sorting in chronological order all records by start date) recorded in the 'Macitentan treatment log' eCRF page. If this date is missing and the subject did not discontinue study treatment, EOM is imputed with the cutoff date. Handling of missing EOM date is described in section 12.

The 'End-of-SoC (EOSoC) date' is defined only for subjects randomized to SoC. EOSoC is taken from the 'Premature Discontinuation of planned SoC' e CRF page. In case the subject did not discontinue the SoC treatment or the date is missing in the related eCRF page, the rules in section 12 have to be followed.

The 'End-of-Randomized-Treatment date / Last intake of randomized study drug date' is the End-of-Macitentan date for subjects randomized to macitentan and subjects < 2 y.o. who are assigned to macitentan, while it is the End-of-SoC date for subjects randomized to SoC.

The 'End-of-Core-Period (EOCP) date' is defined as the date of the last visit prior to clinical cutoff date for Analysis 2. For subjects ongoing and for subjects prematurely discontinuing study visits but continuing in the study for survival follow-up visits, the cutoff date will be the EOCP. For subjects who died, the date of death will be the EOCP. For subjects prematurely discontinuing the study, the EOS date will be the EOCP, defined below. For subjects lost to follow-up, the date of last contact from 'End of study' eCRF page will be the EOCP.

The 'End-of-Study (EOS) date' is defined as the date on the 'End of study' eCRF page or last survival follow-up contact date or safety follow-up telephone call, whichever occurs last. Handling of missing EOS date is described in section 12.

9.1.2. Baseline

For subjects ≥ 2 y.o., the **'Baseline'** value is defined as the last non-missing value recorded before or on the day of randomization for each endpoint and each subject individually.

For subjects < 2 y.o. who are assigned to macitentan without randomization, baseline is the last non-missing value recorded before or on the date of Visit 2.

When considering the 'Post-crossover to Macitentan period', baseline is the last non- missing value recorded before or on the start of macitentan (initiated at crossover).

For the remainder of the document, the term 'Baseline' refers to these definitions rather than the Baseline visit.

9.1.3. Study Day

The Study Day is defined as the day relative to the day of randomization (or Visit 2 for subjects < 2 y.o.), with the day of randomization/Visit 2 considered as 'Day 1' of the study, the day after randomization/Visit 2 as Day 2 and so forth. There is no 'Day 0' in this study, so the day before the day of randomization/Visit 2 is considered to be 'Day −1'. For subjects randomized to macitentan, subjects < 2 y.o. receiving macitentan without randomization and subjects who cross-

over to macitentan after CEC-confirmed disease progression, safety listings will display the day relative to the first macitentan intake (in case different from the day of randomization or subject not randomized to macitentan) in addition to the Study Day as well as the day relative to the last macitentan intake.

9.1.4. Regular Visit

The regular visits are the scheduled visits to be performed every 12 weeks, so the unscheduled visits, the DP visits, the safety FU, the survival FU, EOCP, premature treatment discontinuation visit and the EOS are not 'regular visits'.

9.2. General statistical methodology

9.2.1. Statistical model for PK variables

The PK endpoints will be analyzed descriptively by timepoint only.

9.2.2. Statistical model for time to event variables

9.2.2.1. Stratified log-rank test

The 2-sided p-value will be obtained by 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 following SAS® code will be used:

```
PROC LIFETEST DATA = dataset ALPHA=0.05;
  TIME time*censor(1);
  STRATA ERA WHO/GROUP=treatment TEST=logrank;
  ODS output HomTestS=_tt;
RUN;

Where:
- 'time' represents the variable containing duration to event/censoring times
- 'censor' represents censoring variable (1=censored, 0=event)
- 'treatment' denotes the treatment group variable (0=SoC, 1=Macitentan)
- 'ERA' denotes the ERA randomization stratum (0=ERA present, 1=ERA absent)
- 'WHO' denotes the WHO FC randomization stratum (0=WHO FC I/II, 1=WHO FC III)
```

Due to the non-parametric nature of this test, no statistical assumptions are required. Nevertheless, the resulting p-value will have to be interpreted with caution if the survival curves cross over time.

9.2.2.2. Adjusted proportional hazards model

The hazard ratio (HR) will be estimated by using the below proportional hazards Cox model adjusting for the same randomization stratification factors.

$$h_{ijk}(t) = h_0(t) * e^{\beta 1*TRTi + \beta 2*ERAj + \beta 3*WHOk},$$

where,

- $h_{ijk}(t)$ denotes the hazard function in treatment group *i*, ERA stratum *j* and WHO FC stratum *k*,
- $h_0(t)$ denotes the baseline hazard function at time *t*,
- TRT_i denotes the treatment group with i=1 for macitentan and i=0 for SoC,
- ERA_j denotes the ERA randomization stratum with j=1 for ERA absent and j=0 for ERA present,
- WHO_k denotes the WHO FC randomization stratum with k=1 for WHO FC=III and k=0 for WHO FC=I or II,
- β's denotes the regression coefficients to be estimated. In particular β_1 represents the treatment effect.

The following SAS® code will be used:

```
PROC PHREG DATA= dataset ALPHA=0.05;
  CLASS treatment ERA WHO / ORDER=formatted;
  MODEL time*censor(1) = treatment ERA WHO/ TIES=exact RISKLIMITS;
RUN;

Where:
- 'time' represents the variable containing duration to event/censoring times
- 'censor' represents censoring variables (1=censored, 0=event)
- 'treatment denotes the treatment group variable (0=SoC, 1=Macitentan)
- 'ERA' denotes the ERA randomization stratum (0=ERA present/ 1=ERA absent)
- 'WHO' denotes the WHO FC randomization stratum (0=WHO FC I/II, 1= WHO FC III)
```

This model relies on the hazard proportionality assumptions for each factor. These assumptions will be therefore assessed separately for treatment group, ERA and WHO FC factors by plotting the log of negative log of estimated survivor functions versus the log of time. This diagnostic will be included as a supporting document for the CSR.

9.2.2.3. Unstratified log-rank test

The 2-sided p-value will be obtained by using a 2-sided unstratified log-rank test.

The following SAS® code will be used:

```
PROC LIFETEST DATA=dataset ALPHA=0.05;
   TIME time*censor(1);
   STRATA treatment;
   ODS output HomTests=_tt;
RUN;

Where:
- 'time' represents the variable containing duration to event/censoring times
- 'censor' represents censoring variable (1=censored, 0=event)
- 'treatment' denotes the treatment group variable (0=SoC, 1=Macitentan)
```

Due to the non-parametric nature of this test, no statistical assumptions are required. Nevertheless, the resulting p-value will have to be interpreted with caution if the survival curves cross over time.

9.2.2.4. Unadjusted proportional hazards model

The HR will be estimated by using the below unadjusted proportional hazard Cox model.

$$h_i(t) = h_0(t) * e^{\beta 1 * TRTi},$$

where,

- $h_i(t)$ denotes the hazard function in treatment group *i*,
- $h_0(t)$ denotes the baseline hazard function at time *t*,
- TRT_i denotes the treatment group with i=1 for macitentan and i=0 for SoC,
- β_1 denotes the regression coefficient to be estimated, related to the treatment effect.

The following SAS® code will be used:

```
ODS OUTPUT ParameterEstimates=_freq;
PROC PHREG DATA=dataset ALPHA=0.05;
  CLASS treatment / ORDER=formatted;
  MODEL time*censor(1) = treatment / TIES=exact RISKLIMITS;
RUN;

Where:
- 'time' represents the variable containing duration to event/censoring times
- 'censor' represents censoring variable (1=censored, 0=event)
- 'treatment' denotes the treatment group variable (0=SoC, 1=Macitentan)
```

This model relies on the hazard proportionality assumptions for treatment group factor. This assumption will be therefore assessed by plotting the log of negative log of estimated survivor functions versus the log of time. This diagnostic will be included as a supporting document for the CSR.

9.2.2.5. Cox regression model

The HR will be estimated by using the below Cox regression model adjusting for categorical and continuous covariates.

$$h_{ijk\ldots m}(t) = h_0(t) * e^{\beta 1 * TRTi + \beta 2 * FCT1j + \beta 3 * FCT2k + \ldots + \beta k * FCTml + \beta(k+1) * V_1 + \ldots + \beta(k+n) * Vn},$$

where,

- $h_{ijk\ldots m}(t)$ denotes the hazard function in treatment group *i*, FCT_1 stratum value *j*, FCT_2 stratum *k,…* and FCT_m stratum *l*, individual covariate value V_1, …, and individual covariate value V_m.

- $h_0(t)$ denotes the baseline hazard function at time *t*,
- TRT_i denotes the treatment group with i=1 for macitentan and i=0 for SoC,
- FCT_{ju} denotes the FCT_j categorical covariate with u=0 for reference level, u=1 to n_j for others levels,
- V_1 denotes the value of the covariate V_1 of each subject,
- β's denotes the regression coefficients to be estimated. In particular β_1 represents the treatment effect.

The following SAS® code will be used:

```
PROC PHREG DATA=dataset ALPHA=0.05;
  CLASS treatment FCT1-FCTm / ORDER=formatted;
  MODEL time*censor(1) = treatment FCT1-FCTm V1-Vn / TIES=exact RISKLIMITS;
RUN;

Where:
- 'time' represents the variable containing duration to event/censoring times
- 'censor' represents censoring variable (1=censor, 0=event)
- 'treatment' denotes the treatment group variable (0=SoC, 1=Macitentan
- 'FCT1-FCTm' denote the categorical covariates
- 'V1-Vn' denote the continuous covariates
```

9.2.2.6. Kaplan-Meier estimation and display of survival distributions

A graphical estimate of the survival function for both treatment groups will be obtained by the Kaplan-Meier (KM) product-limit method as implemented in SAS® PROC LIFETEST.

The graphical presentation will apply the following recommendations:

- The KM curves going downwards.
- Termination of the horizontal axis when the number of subjects at risk falls below 10% of the total number of subjects in the analysis set.

The 2-sided 6 monthly 95% confidence intervals (CIs) calculated, based on the exponential Greenwood's formula (Collett 1994) for the standard error (CONFTYPE=LOGLOG in proc LIFETEST), will be drawn and added to the plot. A separated summary table displaying the 6 monthly KM estimates and associated 95% CIs will also be generated.

In addition, the 2-sided p-value obtained from the stratified log-rank and the HR and associated two-sided (1- α)% CI estimated using the adjusted proportional hazards model will be displayed. If reached, the median time to event (as well as 25th and 75th percentiles) for each treatment group will also be provided along with 2-sided CIs calculated using the method of (Brookmeyer 1982). The median time to event will be expressed in months, dividing the value in days by 30.4375.

9.2.3. Statistical methods for dichotomous variables

9.2.3.1. Stratified logistic regression

The 2-sided p-value as well as the odds ratio estimate and its associated 2-sided 95% CI will be obtained by using a logistic regression model stratified on the 2 randomization stratification factors.

The following SAS® code will be used:

```
PROC LOGISTIC DATA=dataset;
  BY visit;
  CLASS treatment;
  MODEL y (event='’WHO FC I/II’ ') =treatment ;
  STRATA ERA WHO;
  ODDSRATIO treatment / cl;
RUN;
```

Where:
- 'treatment' denotes the treatment group variable (0=SoC, 1=Macitentan)
- 'variable' represents the dichotomous variable of interest
- 'ERA' denotes the ERA randomization stratum (0=ERA present, 1=ERA absent)
- 'WHO' denotes the WHO FC randomization stratum (0=WHO FC I/II, 1=WHO FC III)

This model will be used for “WHO FC I or II” endpoint only (Section 10.11.2.1).

9.2.3.2. Profile over time

A graphical representation of the profile over time will be provided by plotting, for each treatment group and timepoint of assessment, the percentages of subjects by category using histograms. The number of values analyzed at each timepoint of assessment will be indicated for each treatment group. The x-axis will not display the timepoints of assessment performed when less than 10% of the subjects in macitentan arm (in the analysis set) are still ongoing regular visits.

9.2.4. Statistical methods for continuous variables

9.2.4.1. Repeated measures mixed model

The 2-sided p-value as well as the SoC-corrected treatment effect will be calculated by using a repeated measures mixed model with treatment, visit, treatment by visit interaction, the 2 randomization stratification factors and baseline value as fixed effects, and subject as random effect. Mixed models will be used to handle missing data under missing at random (MAR) assumption.

For all endpoints, all scheduled visits up to Week 48 will be included in the model. Visits occurring after Week 48 will be included in the model only if at least 10% of subjects randomized to macitentan have a corresponding value for that visit.

An ‘unstructured’ covariance matrix will be used as it does not stipulate any predefined covariance matrix structure. If convergence problems arise the following order of matrix will be applied: Heterogeneous TOEP (TOEPH), Toeplitz (TOEP), Autoregressive(1) (AR(1)). This process will

be repeated for each endpoint. The matrix used for the main model, will be used also for subsequent analyses of the related endpoint (if expected). If using the selected matrix for subsequent analyses this will not converge, "Convergence criteria is not met" will be declared. Covariance matrix structure will be opportunely specified in related footnote table and SAS model output will be saved.

The estimates from this model are then displayed only at the same timepoints of interest.

The following SAS® code will be used:

```
ODS OUTPUT ESTIMATES=trtdiff;

PROC MIXED DATA=dataset ORDER=FORMATTED METHOD=reml;
CLASS subject trt visit ERA WHO;
MODEL value = trt visit trt*visit ERA WHO baseline / noint ddfm=KR solution ;
REPEATED visit /sub = subject type = UN;
LSMEANS trt*visit / CL ;

/* EXAMPLE FOR THE WEEK X CORRESPONDING TO THE 3rd VISIT POST BASELINE
IN A DATASET CONTAINING A TOTAL OF 5 POST BASELINE VISITS */

ESTIMATE "Maci. vs. SoC at Week x" trt -1 1 trt*visit 0 0 -1 0 0 0 01 0 0 / cl;.

/* ESTIMATING THE OVERALL TREATMENT EFFECT */
LSMEANS trt / CL
ESTIMATE "Maci. vs. SoC overall" trt -1 1 / cl;
run;
```

Where:

- 'trt' denotes the treatment group variable (0=SoC, 1=Macitentan)
- 'value' represents the change from baseline to each timepoint of interest
- 'visit' represents the visit variable
- 'subject' represents subject variable
- 'ERA' denotes the ERA randomization stratum (0=ERA present, 1=ERA absent) as per IRT stratification factor
- 'WHO' denotes the WHO FC randomization stratum (0=WHO FC I/II, 1=WHO FC III) as per IRT stratification factor
- 'baseline' represents the baseline value of the variable of interest

- type = UN will change according convergence
- The contrast (-1 and 1 numbering) in the "ESTIMATE" statement will change according number of visits included in the model according the rule "only post-week 48 visits with at least 10% of subjects randomized to macitentan having a corresponding non-missing value at that visit are included in the model".

This model mainly relies on the assumption of normality of the random errors. Therefore, it will be verified by plotting studentized residuals versus predicted individual values as well as stem-and-leaf plot, normality probability plot and box plot. The homoscedasticity will be also assessed

using the studentized residuals graph. This diagnostic will be included as a supporting document for the CSR.

The same model will be also run without including stratification factors as fixed effect as explained in section 10.11.1.4.

9.2.4.2. Profile over time

A graphical representation of the profile over time will be provided by displaying, for each treatment group and timepoint of assessment, box-and-whisker plots. The number of values analyzed at each timepoint of assessment will be indicated for each treatment group. The x-axis will not display timepoint of assessment performed when less than 10% of the subjects in macitentan arm (in the analysis set) are still ongoing regular visits.

10. STATISTICAL ANALYSES

10.1. Overall testing strategy

The analysis of the primary PK variable will be presented by descriptive summaries and no hypothesis testing will be performed.

The analysis of secondary and exploratory endpoints will be presented using p-values compared to the nominal 0.05 2-sided alternative (where applicable) as this is not a formal significance conclusion

There is no multiplicity control for secondary endpoints.

10.2. General rules for data presentations

Individual subject listings will be provided for all PK, safety and efficacy endpoints, as well as for baseline and other subject characteristics. Each listing will be broken down by the following: randomized macitentan, randomized SoC, macitentan cohort < 2 years old, and by country, site, subject number, and assessment date as appropriate.

For listing on SoC subjects crossing over to macitentan, the treatment shown will be: Crossover Macitentan

Data will be summarized by appropriate descriptive statistics (tables or figures), including:

- *Time-to-event variables:*

  Number of subjects having experienced the event, number of censored subjects, number of subjects at risk for the event and 6 monthly KM estimates along with 95% CI based on the exponential Greenwood's formula (Collett 1994) for the standard error,

- *Continuous variables:*

Number of non-missing observations, mean, standard deviation (SD), minimum, Q1, median, Q3 and maximum for continuous variables,

- *Categorical variables:*

  Number of non-missing observations and frequency with percentage per category (unless stated otherwise, percentages based on the total number of observations including observations missing) for categorical variables.

10.3. Display of subject disposition, protocol deviations and analysis sets

10.3.1. Subject disposition

The number of 'Subjects Screened' will be summarized along with the number and percentages of 'Subjects Re-Screened', 'Screening Failures' as well as reasons for failure, 'Enrolled subjects < 2 years old', and 'Randomized Subjects ≥ 2 years old' with percentages based on the SCR will be summarized. Also the number of subjects ongoing Screening (screened but not failing screening nor enrolled/randomized) at the time of data cut will be shown.

Other subject disposition data will be summarized as stated in Section 5.1 based on the FAS3.

An additional disposition output for the categories applicable to the <2 years old population will be produced based on the FAS2.

In addition, the number and percentages of randomized subjects ≥ 2 years old and of enrolled subjects < 2 years old receiving macitentan will be provided by country and site, based on the FAS1 and FAS2, respectively.

Subject disposition will be listed for all subjects in the FAS3, with a flag for subjects in PK Set 1.

10.4. Protocol deviations

Major PDs will be summarized on the FAS3 and PK Set 1 by categories as defined in Section 6, displaying counts and percentages of subjects with at least one PD by randomized treatment group and overall.

All reported PDs defined in the "TOMMOROW_Study_Deviation_Rules_Document" will be listed for all subjects in the FAS3, including a flag for each major PD (defined as significant in the PD Rules document) and a flag for exclusion from PK sets.

Additionally major PDs related to natural disaster/major disruption/pandemic will be summarized and listed separately.

10.5. Analysis sets

Analysis sets are summarized as follows:

- Subjects in the SCR,
- Subjects in the FAS1,

- Subjects in the FAS2,
- Subjects in the FAS3,
- Subjects in the SAS1,
- Subjects in the SAS2,
- Subjects in the SAS3,
- Subjects in the PK Set 1,
- Subjects in the PK Set 3

Definitions of the analysis sets are provided in Section 7. For each analysis set, subjects are displayed by randomized treatment group (or macitentan treatment for subjects < 2 y.o.), distinguishing, for subjects randomized to macitentan, the ones actually treated with macitentan versus the ones untreated. Reasons for exclusion of subjects from analysis sets are summarized per analysis set.

The number and percentage of 'Subjects included' and 'Subjects excluded' from the FAS3 or the SAS will be summarized, and percentages will be based on the FAS3.

A listing of all subjects in the SCR will be provided detailing their analysis set inclusion.

10.6. Analysis of subject characteristics

10.6.1. Demographics

Demographics will be summarized on the PK set 1 and FAS2 overall, and on the FAS1 by treatment and overall. In addition, demographics will be summarized for age, sex and race subgroup defined in Section 8.

Demographics will be listed on the FAS3 with a flag for PK set 1.

10.6.2. Stratification variables

Concordance contingency tables crossing the stratification factors values entered in IRT versus the real values documented in eCRF (WHO FC) or derived based on PD (ERA planned/ongoing) will be provided, based on FAS1.

10.6.3. Baseline disease characteristics

Baseline disease characteristics will be summarized on the PK set 1 and FAS2 overall, and on the FAS1 by treatment and overall. In addition, baseline disease characteristics will be summarized for each subgroup defined in Section 8.

Baseline disease characteristics will be listed on the FAS3 with a flag for PK1.

10.6.4. Other baseline characteristics

Other baseline disease characteristics will be summarized on the FAS1 by treatment and overall.

Other baseline disease characteristics will be listed only within the global QoL and physical activity listings (see Section 5.5).

10.6.5. Medical history

All medical history will be reported in the subject listings for the FAS3 with a flag for PK1 set.

Medical history will be summarized on FAS2 overall and on the FAS1 by treatment group and overall, by System Organ Class and PT.

10.6.6. Previous and study-drug concomitant therapies

All previous and concomitant therapies will be reported in the subject listings based on the FAS3 with a flag for PK1 set. Previous and study-drug concomitant therapies will be flagged accordingly with different symbol.

Previous and study-drug concomitant therapies will be summarized (separately) on the PK set 1 and FAS2 overall, and on FAS1 by treatment group and overall, by ATC classification system and PT.

Study-drug concomitant therapies (defined in Section 5.7.2) and PAH-specific concomitant therapies (defined in Section 5.7.3), will be summarized according to the following periods:

- *"Overall core period"*
- *"Main treatment period"*
- *"Post-crossover to macitentan period":* only for subjects randomized to SoC and who receive macitentan after CEC-confirmed disease progression (crossovers).

For each period, start/end period dates are explained in Section 5.7.2.

Study-drug concomitant therapies will be summarized by ATC classification system and PT on the PK set 1, on the Subset of Crossover Subjects in the FAS1 and on FAS2 overall, and on the FAS1 by treatment group.

PAH-specific concomitant therapies will be summarized by PT on the FAS2 overall, and on the FAS1 by treatment group.

Additionally, study-drug concomitant medications for COVID-19 infection will be summarized and listed.

10.7. Analysis of study treatment exposure and compliance

10.7.1. Duration of treatment

The duration of randomized treatment (for subjects ≥ 2 y.o.) will be presented for subjects in SAS1. Duration of treatment with macitentan (assigned without randomization for subjects <2 y.o.) will be presented on SAS2 separately. All variables will be treated as continuous. In addition, the cumulative distribution of duration of treatment by different interval categories (i.e., at least 3

months, at least 6 months, then every 6 months thereafter) will be tabulated to show counts and percentages of subjects in each interval category. The sum of duration of treatment in years across all subjects exposed to randomized macitentan or SoC or macitentan (subjects < 2 y.o.) will be also displayed as subject-year exposure.

The duration of macitentan treatment for crossover subjects will be similarly presented.

Macitentan exposure data will be listed for all subjects on the SAS3.

Macitentan interruptions due to natural disaster/major disruption/pandemic will be listed on the SAS3.

10.7.2. Drug accountability and compliance with macitentan

The reasons for non-compliance with randomized macitentan will be summarized at each assessment visit as categorical variable for subjects from the SAS1 randomized to macitentan (see Section 10.2).

The same analysis will be performed for non-compliance with macitentan for subjects < 2 y.o. assigned to macitentan without randomization on SAS2 and for the subset of crossover subjects.

Additionally, reasons for non-compliance for all subjects who receive macitentan at any time (randomized (≥ 2 y.o,), assigned (subjects < 2 y.o.) and crossover subjects) for subjects impacted by natural disaster, major disruption or pandemic will be summarized on SAS3.

Number of subjects for whom at least one reason for non-compliance is present are summarized on SAS1 for subjects randomized to macitentan, on SAS2 and on the subset of crossover subjects.

Compliance (based on drug accountability) will also be listed for all subjects in the SAS3.

An individual listing will detail the cases of treatment dispensation errors (discrepancy between allocated/re-allocated and dispensed blister numbers) collected in eCRF page ‘Drug Dispensing & Accountability’, if any, for subjects in the FAS3.

10.7.3. Macitentan or SoC discontinuation

Subjects discontinuing randomized macitentan or SoC (subjects ≥ 2 y.o.) permanently will be summarized on SAS1 along with associated reasons for discontinuation. For each reason, percentages will be based on the number of subjects in each treatment arm.

Subjects < 2 y.o. discontinuing assigned macitentan will be similarly summarized on the SAS2.

In addition, subjects discontinuing macitentan initiated at crossover will be summarized on the subset of crossover subjects in the SAS1 along with reasons for discontinuing macitentan. For each reason, percentages will be based on the number of subjects having initiated macitentan at crossover.

All subjects who prematurely discontinued randomized macitentan or SoC or non-randomized macitentan (<2y.o.) will be listed on the SAS3.

A similar listing on SAS1 will be provided for crossover subjects discontinuing macitentan.

Subjects who discontinued macitentan due to natural disaster, major disruption, or pandemic and subjects who had a first confirmed disease progression event will be flagged in the listings.

10.8. Analysis of duration of follow-up

10.8.1. Duration of time on regular visits

The duration of time on regular visits (weeks) will be summarized on the FAS3 (by randomized treatment group and overall) and on FAS2 (overall) separately.

Subjects who prematurely withdrew from regular study visits will be listed on FAS3. Withdrawals due to natural disaster, major disruption or pandemic will be flagged.

10.8.2. Duration of time on study

The duration of time on study (weeks) will be summarized on the FAS3 and on FAS2 separately by randomized treatment group and overall (see Section 10.2).

The duration of time on study will be listed together with the duration of time on regular study visits.

10.9. Analysis of reasons for early study withdrawal

Subjects withdrawing from the study early will be summarized on the FAS3, by treatment and overall, along with the reasons for withdrawal from the study. For each reason, percentages will be calculated based on the number of subjects in the treatment group and analysis set.

Subjects who prematurely withdrew from the study will be listed on FAS 3. Withdrawals due to natural disaster, major disruption or pandemic will be flagged.

10.10. Analysis of the primary variable

Trough plasma concentrations of macitentan and ACT-132577 at Week 12 (subjects ≥ 2 y.o.) and Week 4 (subjects < 2 years old) will be summarized by body weight, age group and overall ≥ 2 y.o. and by age group only for subjects < 2 y.o., using arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), coefficient of variation (CV) and 2-sided 95% CI of the mean.

The age groups for ≥ 2 y.o. are defined in section 8 and they will be based on the age at screening.

Because the exact date of birth of each subject is not collected, the age groups for < 2 y.o. will be based on the following pragmatic approach if the Week 4 sample is evaluable:

- If the subject has a 1 mg daily dose administered at Visit 2 then the age category is < 6months

- If the subject has a 2.5 mg daily dose administered at Visit 2 then the age category is ≥ 6 months/< 24 months

If the Week 4 sample is not available and the Week 8 sample is used, the age groups for < 2 y.o. will be:

- If the subject has a 1 mg daily dose administered at Week 4 then the age category is < 6months

- If the subject has a 2.5 mg daily dose administered at Week 4 then the age category is ≥ 6 months/< 24 months

- If the subject has a daily dose > 2.5 mg administered at Week 4 this means that the subject is more than 2 y.o at Week 4 and the additional age category is ≥ 24 months

The body weight groups for the PK analysis are:

[10 kg, 15 kg)

[15 kg, 25 kg)

[25 kg, 50 kg)

≥ 50 kg

The body weight assessments used for grouping is those closer (occurred in the same day or before) to the macitentan dosing preceding the trough plasma concentration assessment (i.e. at day 1 or before).

PK variables will be listed on the PK set 1 for subjects ≥ 2 y.o and on the PK set 3 for subjects < 2 y.o.

10.11. Analysis of the secondary efficacy variables

On subjects of the FAS1 (subjects ≥ 2 y.o.), treatment effect estimates, 95% CLs and p-values will be provided for exploratory purposes only. No multiplicity adjustment will be applied for the multiple analysis timepoints. 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 secondary efficacy variables will include descriptive analyses only for subjects of the FAS2 (< 2 y.o. receiving macitentan).

10.11.1. Analysis of the time to event efficacy variables

The analysis of these endpoints will be performed according to the intent-to-treat principle.

10.11.1.1. Hypothesis and statistical model

The null and alternative hypotheses are formulated in terms of difference between survival distributions and are expressed according to the non-parametric log-rank test.

$S_{dp,macitentan}(t)$ denotes the survival distribution of the probability of being free of event up to time t in macitentan group.

$S_{dp,SoC}(t)$ denotes the survival distribution of the probability of being free of event up to time t in SoC group:

H_0: $S_{dp,macitentan}(t) = S_{dp,SoC}(t)$, for all $t \geq 0$

H_A: $S_{dp,macitentan}(t) \neq S_{dp,SoC}(t)$, for at least one $t \geq 0$.

The p-values from all hypothesis tests are exploratory in nature and are not a formal significant conclusion.

10.11.1.2. Handling of missing data

Due to the nature of the time to event efficacy variables, subjects with no CEC-confirmed event have their time to event 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 KM product-limit method and discussed in a supporting document for the CSR.

Table 5 illustrates different possible cases and the outcome for time to CEC-confirmed disease progression analysis.

Table 5: Different possible cases and outcome for time to CEC-confirmed 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 EOCP	Date of first documented disease progression or death	Event
	No disease progression up to EOCP	Earliest between EOCP date and cutoff date for respective analysis	Censored *Reason:* Core Period completed
Subject prematurely discontinues	Disease progression documented during a regular study visit up to EOCP	Date of first documented disease progression	Event

Table 5: Different possible cases and outcome for time to CEC-confirmed disease progression analysis

Compliance to study Follow-up	Situation*	Date of disease progression or censoring	Outcome
regular study visits during core period AND completes survival follow-up until EOCP	No disease progression during regular study visits of core period AND death during core period	Date of death	Event
	No disease progression during regular study visits of core period AND no death during core period	Earliest between last survival follow-up contact date, EOCP and cutoff date for respective analysis	Censored *Reason:* Core Period completed
Subject prematurely discontinues regular study visits and/or survival follow-up before EOCP[1]	Disease progression documented during a regular study visit up to EOCP	Date of first documented disease progression	Event
	No disease progression during regular study visits of core period AND death during core period	Date of death	Event
	No disease progression during regular study visits of core period AND no death during core period	Earliest between last regular study visit and last survival follow-up contact date	Censored *Reason:* as reported during'End of Core Period' visit

* All disease progressions have to be CEC-confirmed
[1] Participants who have prematurely discontinued the study are considered in this scenario
CEC = Critical Event Committee; eCRF = electronic case report form; EOCP = End-of-Core Period.

For all other time to event secondary efficacy variables, the handling of missing/censored data rule is described directly in the definition of each of these variables (see Section 5.12.1).

10.11.1.3. 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 on the FAS1 (see Section 9.2.2.1). 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 randomization stratification factors (see Section 9.2.2.2). Estimate of HR and its associated 95% CI will be displayed.

KM estimates will be calculated with 2-sided 95% CIs 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 (see Section 9.2.2.6). 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.

10.11.1.4. Supportive/sensitivity analyses

The following supportive analyses are planned (based on FAS1, if not otherwise stated) for the time to CEC-confirmed disease progression:

1. Main analysis censoring at the last regular visit (during the core period) performed + 7 days
   - A subject with a CEC-confirmed disease progression > 7 days after his/her last regular study visit was performed, is right-censored at the last regular study visit date + 7 days),
   - A subject without any CEC-confirmed disease progression AND censored date > 7 days after his/her last regular study visit was performed, is right-censored at the last regular study visit date + 7 days),
2. Main analysis without adjustment for randomization stratification factors,
3. Main analysis based on investigator reporting.
4. Sensitivity analysis to assess impact of natural disaster, major disruption or pandemic, excluding subjects with natural disaster, major disruption or pandemic-related AEs or CEC-confirmed death due to COVID-19 (for the main analysis).
5. An analysis using the stratification factors as collected in eCRF (WHO FC) or gathered from PDs (ERA treatment ongoing/planned).

10.11.1.5. Subgroup analyses

In order to assess the consistency of the treatment effect across different subject subgroups for the time to CEC-confirmed disease event secondary efficacy variable, a subgroup analysis will be performed, based on the FAS1, on subgroups defined in Section 8.

Subgroup analysis will be performed with a separate analysis for each subgroup variable using an un-stratified proportional hazards regression model with treatment, subgroup and treatment-by-subgroup interaction terms.

The test of interaction is performed with ‘n-1’ degrees of freedom where ‘n’ is the number of subgroup categories. If the interaction term is significant at the 0.01 level then the treatment effect, measured as an HR, will be estimated within each level of the subgroup variable based on the Cox model including the interaction term. If the interaction term is not significant at the 0.01 level (2-sided) then the treatment effect HR and corresponding 95% CIs will be estimated using a separate proportional hazards regression models (without interaction) for each level of the subgroup variable.

Treatment effect HR and corresponding 95% CIs for the different levels of each subgroup are presented in a forest plot. The forest plot is prepared as described in (Cuzick 2005) with a vertical reference line displayed at the level of the overall treatment effect for macitentan versus SoC and a vertical reference line at HR = 1. The p-value for the interaction test is displayed on the plot for each subgroup along with the number of subjects/events in macitentan and the number of subjects/events in SoC within each subgroup level.

No multiplicity adjustment will be introduced; the subgroup analysis is descriptive in nature.

10.11.1.6. Descriptive analyses

The following descriptive analyses will be performed on subjects of the FAS1 and FAS2 (listings only) separately to support clinical interpretation:

- *Component distribution*: number and percentage of subjects by category of 'first CEC-confirmed disease progression':
  - Death (all causes),
  - Atrial septostomy or Potts' anastomosis, or registration on lung transplant list,
  - Hospitalization due to worsening PAH,
  - Clinical worsening of PAH
- *Concordance analysis for the type of first disease progression*: summary of agreement/disagreement for disease progression between investigators and CEC diagnoses for the nature of the first disease progression.

  This analysis is performed on the FAS1 only.
- *Reasons for censoring for each time to event variable*: number and percentage of subjects by reason for censoring:
  - Study completed,
  - Lost to follow-up,
  - Study withdrawal: Parent/Subject decision,
  - Study withdrawal: Physician decision,
- Median time to censoring, for subjects without each CEC-confirmed event up to EOCP,
- Median time to premature censoring, for subjects who prematurely discontinued the study (i.e., reason for censoring is different from 'study completed') without each CEC- confirmed event.

The median time to censoring and premature discontinuation will be expressed in months, dividing the value in days by 30.4375.

10.11.2. Analysis of the other secondary efficacy variables

The analysis of other secondary variables will be carried out on the FAS1 (subjects ≥ 2 y.o.) and will consider values collected up to the end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects.

The analyses will only be descriptive for subjects of the FAS2 (< 2 y.o. receiving macitentan).

10.11.2.1. WHO FC I or II (yes/no) at Weeks 12, 24

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 only at Weeks 12 and 24 by means of a stratified logistic regression on FAS1. The 2 stratification factors will be: ongoing/planned ERA treatment (yes vs no) as per IRT stratification factor 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% CIs (see Section 9.2.3.1).

In addition to the stratified analysis, an unstratified logistic regression will be performed. Plot of WHO FC (I/II versus III/IV) profile over time will be provided (see Section 9.2.3.2).

In case of missing Week 12 values, in the logistic regression, subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 12 (i.e. hospitalized before Week 12 visit date or died prior to last day of the related time-window), the value of WHO FC will be imputed as the worst case (e.g., IV) at Week 12 for analysis. The same imputation rule is applied for subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 24, but imputing the worst case at Week 24.

Shift from baseline in WHO FC (including grouped FC I/II and III/IV) at each time point will be displayed descriptively on the FAS 1 and FAS2 separately.

The percentage of subjects with WHO functional class I or II at each time point be also graphically presented on FAS1 via histogram.

A listing of WHO FC at each timepoint will be provided on the FAS3.

10.11.2.2. Percent of baseline in plasma NT-proBNP (pmol/L) at Weeks 12, 24

The percent of baseline in NT-proBNP at each timepoint of assessment will be evaluated with the use of a repeated measures mixed model on the log-transformed percent of baseline in NT-proBNP between the timepoint and baseline on FAS1. 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 fixed covariate, while subject will be included as a random effect (see Section 9.2.4.1). Each timepoint of assessment will be assessed with the comparison at Week 12 and 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.

The model is re-run without the interaction term to also present the overall averaged treatment effect with 2-sided 95% CI and p-value.

In addition, the same repeated measures mixed model will be performed considering the vector of observed changes from baseline in NT-proBNP (original scale) values at each timepoint of assessment, using the same covariance matrix of the model on log-transformed percent of baseline.

Plot of NT-proBNP profile over time will be provided on FAS1 considering observed NT-proBNP changes from baseline (original scale [see Section 9.2.4.2]).

Change from baseline and percent of baseline in NT-pro BNP at each timepoint of assessment will be descriptively summarized on FAS1 and FAS2 separately.

A listing of NT-pro BNP values will be provided on FAS3.

10.11.2.3. Mean daily time spent in moderate to vigorous physical activity as measured by accelerometry at Week48

Changes from Baseline in mean daily time spent in moderate to vigorous physical activity as measured by accelerometry variables defined in Section 5.12.1.7 will be analyzed over time by means of a repeated measures mixed model on values at each visit on FAS1. The model will include randomized treatment, visit, treatment by visit interaction, the 2 randomization stratification factors as fixed effects and the baseline value as a fixed covariate, while subject will be included as a random effect (see Section 9.2.4.1).

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.

The model is re-run without the interaction term to also present the overall averaged treatment effect with 2-sided 95% CI and p-value.

Descriptive statistics on FAS1 will also be presented.

Plots over time will be provided considering observed changes from baseline in mean daily time spent in moderate to vigorous physical activity (see Section 9.2.4.2) for the FAS1.

10.11.2.4. Echocardiography variables at Week 24

The changes from Baseline to Weeks 12 and 24 in echocardiographic variables defined in Section 0 will be described by means of repeated measures mixed model on FAS1 as described for physical activity variables in Section 10.11.3.2.

Each timepoint of assessment will be assessed with the comparison at Week 24 being the main comparison.

Plots of echocardiography variables profiles over time will be provided on FAS1 considering observed changes from baseline (see Section 9.2.4.2).

The change from Baseline to Weeks 12 and 24 in echocardiographic variables will be summarized descriptively on the FAS1 and FAS2.

The echocardiographic variables and change from baseline will be provided in a listing on the FAS3.

10.11.2.5. Quality of Life As Measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15) at Week 24

The changes from Baseline in QoL variables as measured by the PedsQL™ 40 Generic Core Scales Short Form (SF15) variables (defined in Section 5.12.1.9) will be described by means of repeated measures mixed model on FAS1 as described for physical activity variables in Section 10.11.3.2.

Each timepoint of assessment will be assessed with the comparison at Week 24 being the most relevant.

The changes from Baseline in QoL variables will be also descriptively summarized and graphically presented on the FAS1.

10.11.3. Analysis of the exploratory variables

The analysis of exploratory variables will be carried out on the FAS1 (subjects ≥ 2 y.o.) and will consider values collected up to the end of randomized macitentan or SoC + 7 days, or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects.

The analysis of these exploratory variables will only be descriptive for subjects of the FAS2 (< 2 y.o. receiving macitentan).

10.11.3.1. Panama FC I or II (yes/no) at Week 24

The proportion of subjects will be analyzed at each timepoint of assessment using the same methods outlined in Section 10.11.2.1 for the WHO FC endpoint for the FAS1, without imputation for missing values.

Shift from baseline in Panama FC (including grouped FC I/II versus IIIa/IIIb/IV) at each time point will be displayed descriptively on the FAS 1 and FAS2 separately.

The proportion of subjects with Panama FC I/II at each timepoint of assessment will be also graphically presented on FAS1 via histogram.A listing of Panama FC at each timepoint of assessment will be provided on the FAS3.

10.11.3.2. Other Physical activity variables (accelerometry) at Weeks 12, 24 and 48

Changes from Baseline in the additional accelerometry variables defined in Section 5.12.2.2 will be analyzed over time by means of a repeated measures mixed model on values at each visit on FAS1. 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 (see Section 9.2.4.1).

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.

The model is re-run without the interaction term to also present the overall averaged treatment effect with 2-sided 95% CI and p-value.

Descriptive statistics on FAS1 will also be presented.

Plots over time will be provided considering observed changes from baseline (see Section 9.2.4.2) for FAS1.

10.11.3.3. Six-minute walk distance at Weeks 12, 24 and 48

Only values collected up to end of randomized macitentan or SoC + 7 days or up to start of macitentan or end of SoC + 7 days, whichever comes first, for crossover subjects will be considered for this analysis. This analysis will only be performed on FAS1 (subjects ≥ 2 y.o.).

The change from Baseline to Weeks 12, 24 and 48 in 6-minute walk distance will be described by means of repeated measures mixed models as described for physical activity variables in Section 10.11.3.2.

Descriptive statistics on FAS1 will also be presented. Plots of 6-minute walk distance profile over time will be provided considering observed changes from baseline (see Section 9.2.4.2) on FAS1.

10.12. 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 EOCP. Safety variables will be summarized by treatment group on SAS1 and overall on SAS2 and for the subset of crossover subjects. Safety variables will be summarized for the subgroups age, gender and race (Section 8) as further specified.

Three periods of interest are defined as follows:

- *"Overall core period":* from the randomization date (or Visit 2 for subjects < 2 years old) up to end of Core Period
- *"Main treatment period"*: For subjects ≥ 2 y.o., from the randomization date up to end of randomized macitentan or SoC + 30 days (or end of Core period whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first. For subjects < 2 y.o., from Visit 2 up to end of macitentan + 30 days (or end of Core period whichever comes first).
- *"Post-crossover to macitentan period":* only for crossover subjects. From the start of macitentan (initiated at crossover) up to end of macitentan + 30 days or the end of the core period, whichever comes first. For crossover subjects, baseline is the last non- missing value recorded before or on the start of macitentan (initiated at crossover) as defined in section 9.1.2.

Mostly all AEs will be summarized for the "*Overall core period"* and "*Main treatment period"* for all subjects and for the *"Post-crossover to macitentan period"* only for crossover subjects. See section 10.12.1 for the exact details.

Laboratory tests will be summarized in the *"Main treatment period"* and in the *"Post-crossover to macitentan period"* for crossover subjects.

The safety variables: vital signs, growth and sexual maturation, will be summarized only on the *"Main treatment period"*.

10.12.1. Adverse events

All AEs are coded with MedDRA and will be analyzed by randomized treatment arm for SAS1 and overall for SAS2.

AEs with onset during the "*Overall core period",* the "*Main treatment period" and* the *"Post-crossover period"* are summarized according to the **Error! Reference source not found.** below.

The Table describes all the AE analyses that will be produced per type (by SOC and PT vs by PT only) and the analysis sets used.

The age, sex and race subgroups are defined in Section 8.

Table 6

		by SOC and PT			by PT		
		Overall period	Main treatment period	Post Crossover to macitentan period	Overall period	Main treatment period	Post Crossover to macitentan period
AE	SAS1	x	x		x	x	
	SAS2	x	x				
	SAS1Crossovers			x			
AE by age	SAS1		x				
	SAS2						
	SAS1Crossovers			x			
AE by sex	SAS1		x				
	SAS2		x				
	SAS1Crossovers			x			
AE by race	SAS1		x				
	SAS2						
	SAS1Crossovers			x			

SAE	SAS1	x	x		X	x	
	SAS2	x	x				
	SAS1Crossovers			x			
AE leading to premature trt discontinuation	SAS1		x			x	
	SAS2		x				
	SAS1Crossovers			x			
AE with fatal outcome	SAS1	x	x		X	x	
	SAS2	x	x				
	SAS1Crossovers			x			
AE by maximum intensity	SAS1		x				
	SAS2		x				
	SAS1Crossovers			x			
AE by relationship	SAS1 Macitentan		x				
	SAS2		x				
	SAS1Crossovers			x			
SAE by relationship	SAS1 Macitentan		x				
	SAS2		x				
	SAS1Crossovers			x			
AESI	SAS1					x	
	SAS2					x	
	SAS1Crossovers						x
AESI by Age	SAS1					x	
	SAS2						
	SAS1Crossovers						x
AESI by Sex	SAS1					x	
	SAS2					x	
	SAS1Crossovers						x
AESI by Race	SAS1					x	
	SAS2					x	

	SAS1Crossovers						x
AE of interest for Natural disaster, major disruption pandemic	SAS1					x	
	SAS2						
	SAS1Crossovers						
AE of interest for COVID leading to death	SAS1					x	
	SAS2						
	SAS1Crossovers						

The summary tables by SOC and PT on SAS1 will presented in descending order according to the incidence in the macitentan arm (e.g., SOC and PT within each SOC with the highest number of occurrences appears first). Equal frequency of different SOC/PTs will be sorted in alphabetical order of the SOC/PT.

Similarly, summary tables provided by PT on SAS1 will be provided in descending order of incidence in the macitentan arm.

Listings will flag AEs according to the period when they occurred and will be provided for

- all reported AEs on SAS3
- SAEs on SAS3
- AEs leading to premature discontinuation of randomized macitentan or SoC or to AEs leading to premature discontinuation of macitentan initiated at crossover on SAS1
- AEs leading to premature discontinuation of macitentan for subjects < 2 years old on SAS2,
- AEs with fatal outcome on SAS3,
- Natural disaster/Major disruption/Pandemic AEs on SAS3

10.12.2. Deaths

Number of subjects who died and primary cause of death will be summarized on the SAS1 by treatment arm and overall and on the SAS2 overall from randomization (Visit 2 for subjects < 2 y.o.) until EOCP or cut-off date, whichever occurs first.

The summary table will be presented by descending order of PT according to the incidence of deaths in the macitentan arm.

Reported deaths and cause of death will also be listed on SAS3 by treatment group.

Deaths due to COVID-19 infection will be also listed separately on SAS3.

10.12.3. Laboratory tests

MLA occurring during the main treatment period are those with onset during that period and that were not present at baseline in the same or worse category (considering the direction of worsening).

In other words, the MLAs are evaluated independently by direction of worsening (e.g., a post-baseline MLA of "HH" is considered if the baseline is "L" or "LL" or "LLL" (where applicable) or "H", or within normal limits or missing. On the other hand, it is not considered if the baseline is "HH" or "HHH" when applicable).

MLA during the main treatment period are summarized by treatment arm on the SAS1 and overall on the SAS2.

For each category (i.e., LL, LLL, HH, HHH), MLA (see Section 5.13.2) are summarized for each laboratory variable displaying counts and percentages of subjects with at least a MLA. Percentages are calculated as number of subjects with at least one abnormality for the parameter under consideration divided by the number of subjects with any post-baseline laboratory measurement (and for hemoglobin, also with a valid baseline value based on the definition of the abnormality).

Similarly, MLA occurring during the Post-crossover to macitentan period are those with onset during that period and that were not present at the crossover baseline in the same or worse category (considering the direction of worsening).

They are summarized overall for the subset of crossover subjects in the SAS2.

Specifically for erythrocyte count, hemoglobin, hematocrit, AST, ALT, total bilirubin, and alkaline phosphatase absolute values and changes from baseline will be summarized over time by treatment on SAS1, and overall on SAS2 and on the subset of crossover subjects.

Plots of profiles over time will also be provided on SAS1 (see Section 9.2.4.2),

Finally, the emergence of potential Hy's Law cases will be analyzed during the main treatment period (separately on SAS1 and SAS2) and during the post-crossover to macitentan period on the subset of crossover subjects. For each of the following condition, the number and frequency of subjects meeting the condition for at least one post-baseline visit, whereas the same condition was not met at baseline are provided:

- ALT > 3 × upper limit of normal (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.

All available local and central laboratory data will be listed by subject on SAS3.

10.12.4. Vital signs variables: change from baseline over time

Change from baseline in 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 10.11.3.2 on SAS1.

On the SAS2 changes from baseline will be on descriptively summarized.

Box plots of vital signs profiles over time will be provided considering observed changes from baseline by treatment group on SAS1 and overall on SAS2 (see Section 9.2.4.2).

A listing will be provided on SAS3.

10.12.5. Growth variables: change from baseline over time

The change from baseline in growth variables, (body mass index, height/length and weight), will be analyzed over time up to end of randomized macitentan or SoC + 30 days or up to start of macitentan or end of SoC + 30 days, whichever comes first, for crossover subjects by means of repeated measures mixed models as described for physical activity variables in Section 10.11.3.2 for SAS1 only and by descriptive statistics for SAS2.

In addition, body weight (kg) and body height/length (cm) will be plotted over time as individual curves per subject on SAS3. The x-axis will display age in months. The y-axis will display the growth parameter of interest, weight (kg) or height/length (cm). Separate figures will be created for male and female subjects with/without Down Syndrome with overlays of sex-specific standard CDC growth percentiles (https://www.cdc.gov/growthcharts/clinical_charts.htm; https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/documents/DS_Boys_Length_Birthto36mo.pdf; https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/documents/DS_Girls_Length_Birthto36mo.pdf; https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/documents/DS_Boys_Height_2-20years.pdf; https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/documents/DS_Girls_Height_2to20years.pdf) by age for the 5th, 25th, 50th, 75th, and 95th percentiles. All collected values of weight and height/length are used. A different line structure will be used for each treatment group. on SAS3.

A listing of absolute and change from baseline values of growth variables will be provided on SAS3.

10.12.6. Sexual maturation (Tanner stage) and childbearing potential

Sexual maturation as measured by the Tanner stage will be summarized at baseline and each timepoint of assessment on SAS1 only by treatment group.

Listings of sexual maturation and child-bearing potential (females only) will be provided on SAS1.

10.13. Analysis of quality of life variables

The analysis of QoL variables described in section 5.14 will be carried out on the FAS1 (subjects ≥ 2 y.o.)

QoL variables will be analyzed separately depending on subjects or caregivers report across age groups specified in section 8.

Changes from baseline in QoL total scores defined in Section 5.14 will be analyzed over time by means of a repeated measures mixed model as described for physical activity variables in Section 10.11.3.2.

QoL single items and total scores will also be listed on the FAS1.**Error! Reference source not found.**

10.14. Analysis of pharmacokinetic variables

PK concentrations for macitentan and ACT-132577 over 24 hours at pre-dose and following administration of macitentan at steady-state will be summarized using arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, coefficient of variation (inter-subject in %), and 95% CI of the arithmetic and geometric means on the PK3 set.

Additional PK analyses will be provided in a separate report.

10.15. 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 with counts and percentages on macitentan treated subjects in SAS1 and SAS2 separately. No distinction will be done between subjects/caregiver evaluations, assessment will be summarized together.

Palatability and acceptability will be listed in SAS3.

11. GENERAL DEFINITIONS AND DERIVATIONS

In order to minimize missing data and to analyze the data at the relevant planned (scheduled) visits, all recorded assessments for each subject up to EOCP will be reassigned to the most appropriate visit according to the best fitting time window for that visit. Any unscheduled visit will be mapped to a time window. The windows are based on the number of study days between two consecutive planned assessments (84 days) and midpoints will determine new windows. The windows are based on the number of days since randomization corresponding to the date of data record as described in Tables 7-11 below.

Table 7 applies to WHO and PANAMA FCs, NT-proBNP, laboratory and vital signs.

Table 8 applies to physical activity and 6MWT.

Table 9 applies to echocardiography.

Table 10 applies to Quality of life.

Table 11 applies to Tanner stage.

Should more than one assessment fall within the same time window, then the closest value to the planned timepoint will be assigned for presentation in data summaries and analyses. In case of values that are equidistant to the planned timepoint, the later assessment will be considered for the analyses. If more than one value falls on the same day then the worst value will always be used (e.g., for WHO FC the higher value will be used).

For laboratory parameters the date of blood sampling (as recorded in the central laboratory database) will be used to perform the mapping.

Table 7 Time windows for reassignment of WHO and PANAMA FCs, NT-proBNP, laboratory and vital signs

Time point	Study Day	Lower Limit	Upper Limit
Week 4 (only for laboratory and vital signs in <2 y.o.)	28	2	42
Week 8 (only for laboratory and vital signs in <2 y.o.)	56	43	70
Week 12 (only for laboratory and vital signs in <2 y.o.)	84	71	126
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week k (every 12 weeks)	***k*7***	***k*7 – 41***	***k*7 + 42***

Table 8: Time windows for reassignment of physical activity and 6MWT

Time point	Study Day	Lower Limit	Upper Limit
Week 12	84	2	126
Week 24	168	127	252
Week 48	336	253	No limit

Table 9: Time windows for reassignment of echocardiography

Time point	Study Day	Lower Limit	Upper Limit
Week 12	84	2	126
Week 24	168	127	No limit

Table 10: Time windows for reassignment of QoL

Time point	Study Day	Lower Limit	Upper Limit
Week 12	84	2	126
Week 24	168	127	252
Week 48	336	253	504
Week 96	672	505	840
Week k (every 48 weeks)	***k*7***	***k*7 – 167***	***k*7 + 168***

Table 11: Time windows for reassignment of Tanner stage

Time point	Study Day	Lower Limit	Upper Limit
Week 24	168	2	252
Week 48	336	253	420
Week k (every 24 weeks)	***k*7***	***k*7 – 83***	***k*7 + 84***

12. HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

12.1. Treatment start and end date

For subjects randomized to macitentan (subjects ≥ 2 y.o.) or receiving macitentan (subjects < 2 y.o.):

- If the day is missing for macitentan start date, then it will be replaced by day of the randomization date (or date of Visit 2 for <2y.o.), and in case the day of randomization is in the previous month, replace the day by 1.

- If day and month are missing for macitentan start date or if the date is missing entirely and at least an incomplete end date for macitentan is present, replace entirely by the randomization date (or date of Visit 2 for <2y.o.).
- If the day is missing for macitentan end date, then replace by the minimum between:
  - the macitentan end date with day imputed to the last day of the month,
  - the date of EOM visit.
- If the entire date is missing for macitentan end date, then replace by the earliest between:
  - cut-off date,
  - date of last contact from 'End of study' eCRF page
  - date of End of Study from 'End of study' eCRF page
  - date of Death from 'Death' eCRF page.
- If the macitentan end date is partial, then replace by the earliest between:
  - cut-off date,
  - date of last contact from 'End of study' eCRF page
  - date of End of Study from 'End of study' eCRF page
  - date of Death from 'Death' eCRF page
  - upper limit of the range of possible dates.

In case both start and end date of macitentan are missing no imputation is performed.

For subjects randomized to SoC:

- If the entire date is missing for SoC end date and the subject did not cross-over to macitentan and the 'End of Study' eCRF is completed (with Date of End of Study and/or Date of last contact), then replace by the earliest between:
  - cut-off date
  - date of last contact from 'End of study' eCRF page
  - date of End of Study from 'End of study' eCRF page
  - date of Death from 'Death' eCRF page.
- If the entire date is missing for SoC end date and the subject did not cross-over to macitentan and the 'End of Study' eCRF is not completed (with no Date of End of Study and no Date of last contact), then replace by the earliest between:
  - cut-off date
  - date of Death from 'Death' eCRF page
  - end date of the last recorded visit.

- If the SoC end date is partial and the subject did not cross-over to macitentan and the 'End of Study' eCRF is completed (with Date of End of Study and/or Date of last contact), then replace by the earliest between:
  - cut-off date,
  - date of last contact from 'End of study' eCRF page (if it falls in the range of possible dates)
  - date of End of Study from 'End of study' eCRF page (if it falls in the range of possible dates)
  - date of Death from 'Death' eCRF page (if it falls in the range of possible dates)
  - upper limit of the range of possible dates.
- If the SoC end date is partial and the subject did not cross-over to macitentan and the 'End of Study' eCRF is not completed (with no Date of End of Study and no Date of last contact), then replace by the earliest between:
  - cut-off date,
  - end date of the last recorded visit (if it falls in the range of possible dates)
  - date of Death from 'Death' eCRF page (if it falls in the range of possible dates)
  - upper limit of the range of possible dates.
- If the entire date is missing for SoC end date and the subject crossed over to macitentan, then replace by the crossover date
- If the SoC end date is partial and the subject crossed over to macitentan, then replace by the earliest between the crossover date and the upper limit of the range of possible dates

12.2. End of Study date

Type of date	Date is incomplete	Date is missing
End of study date	It is imputed with the end date of the last recorded visit on the eCRF if this falls in the range of possible dates. Otherwise it is imputed with the upper limit.	Replace with the end date of the last recorded visit on the eCRF.

12.3. Study-drug and PAH-specific concomitant therapy dates

Type of date	Date is incomplete	Date is missing

Study-drug concomitant start date	• If the randomization date (or Visit 2 for <2y.o.) falls in the range of possible dates, replace by the randomization date (or Visit 2 for <2y.o.). • Otherwise, replace by the lower limit	Replace by the informed consent date.
Study-drug concomitant end date	If the concomitant therapy start date < randomization date (or Visit 2 for <2y.o.) then • If month and/or year of end date > month and/or year of randomization (or Visit 2 for <2y.o.), use the upper limit; • If month and/or year of end date = month and/or year of randomization (or Visit 2 for <2y.o.): if Ongoing = Y, use randomization date (or Visit 2 for <2y.o.); if Ongoing = N, use the latest between the lower limit and the concomitant therapy start date; • If month and/or year of end date < month and/or year of randomization (or Visit 2 for <2y.o.), replace by the latest between upper limit and randomization date (or Visit 2 for <2y.o.). If the concomitant therapy start date ≥ randomization date (or Visit 2 for <2y.o.) then replace by the upper	Do nothing

12.4. PAH diagnosis date

Type of date	Date is incomplete	Date is missing
PAH diagnosis date	Replace by the earliest date between lower limit and randomization date (or Visit 2 for <2y.o.)	Replace by the informed consent date.

12.5. Adverse event dates

Type of date	Date is incomplete	Date is missing
AE resolution date	The upper limit	No approximation, the AE is considered as ongoing in the analysis
AE onset date	If the end date of the AE is after the randomization date or Visit 2 for <2y.o.), and if the randomization date/ Visit 2 date falls in the range of possible dates, the randomization date/ Visit 2 date is used. In all the other cases, the lower limit is used.	Whichever is the earliest between the date of resolution of the AE and the randomization date/ Visit 2 date

AE = adverse event.

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14. APPENDICES

Appendix 1: Protocol Synopsis

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** To evaluate the pharmacokinetics (PK) of macitentan in children with pulmonary arterial hypertension (PAH). **Secondary objectives** To assess safety and tolerability of macitentan in children with PAH. 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. 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. 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 the 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. 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). 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 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 (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. 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 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.

	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. 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-upuntil EOCP. Only for subjects whose parent(s) / legal representative withdraw consent to further study participation is the safety follow-up telephone call EOS. **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., PTA, LTE study) to allow treatment continuation, if assessed beneficial by the investigator and within local regulations. 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. 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. 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).
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. 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. 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. 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 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 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. 5. PAH belonging to the Nice 2013 Updated Classification Group 1 (including Down Syndrome) and of the following etiologies: • Idiopathic PAH (iPAH) • Heritable PAH (hPAH) • PAH associated with congenital heart disease (CHD):

	– PAH with co-incidental CHD (confirmed by the Baseline Characteristics Adjudication Committee [BCAC]) – Post-operative PAH (persisting/ recurring/ developing ≥ 6 months after repair of CHD) • Drug or toxin-induced PAH • PAH associated with HIV • PAH associated with connective tissue disease (PAH-aCTD) 6. WHO FC I to III 7. PAH-specific treatment-naïve subjects or subjects on PAH-specific treatment (monotherapy 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 reliable method of contraception (if sexually active) up to EOS.
EXCLUSION CRITERIA	**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 modified 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 cytochrome P450 3A (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. 17. Serum aspartate aminotransferase and/or alanine aminotransferase > 3 × upper limit of normal range. 18. Criterion modified per Amendment 6 Version 7: Severe hepatic impairment, e.g., Child-Pugh Class C. 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. 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** 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. Body weight or age for potential dose adjustment will be verified every 12 weeks at scheduled study visits. In subjects ≥ 2 y.o., phosphodiesterase Type 5 (PDE-5) inhibitor is the only allowed PAH-specific background medication until disease progression. In subjects < 2 y.o., oral/ inhaled prostanoid treatment are also allowed as PAH-specific background therapy in all study periods. **Control arm / Standard of Care (SoC)** SoC (including PAH non-specific treatment and/or up to two PAH-specific medications as per local practice) is the control group. 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. 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** 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. 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. **Allowed concomitant therapy** 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.'

	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. SoC group – 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. – 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. Single-arm Extension Period: – Any PAH-specific medication except an ERA can be administered in addition to macitentan. Use of IV prostanoids for vasoreactivity testing is allowed in all study subjects and during all study periods. **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. • 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). • 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.

	• 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. 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: • 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 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: – 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. 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 treatments the investigator should consult respective medication label(s). **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 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. During the SAEP, PAH treatment can be escalated as per local practice.
ENDPOINTS	**Primary endpoint(s)** In subjects ≥ 2 y.o. in the macitentan arm: • Trough (pre-dose) plasma concentrations of macitentan and its active metabolite (ACT-132577) at Week 12 (steady-state conditions) In subjects < 2 y.o. on macitentan: • Trough concentrations of macitentan and its active metabolite (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 and age group in subjects ≥ 2 y.o. and < 2 y.o., respectively. **Secondary efficacy endpoints** The secondary endpoints are: • 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, prostanoids, prostacyclin receptor (IP receptor) agonist, soluble guanylate cyclase stimulator. • 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 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^{TM} 4.0 Generic Core Scales Short Form (SF15). **Exploratory endpoints** • Panama FC status (I or II vs FC III or IV) at Week 24 • 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. 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. **Safety endpoints** Safety endpoints are assessed up to EOS and include: • Adverse events (AEs) • Serious adverse events (SAEs) • AEs leading to premature discontinuation of macitentan or SoC • AEs of special interest • Marked laboratory abnormalities • Change from Baseline in selected laboratory parameters to all timepoints of assessments • Change from Baseline in vital signs (blood pressure, 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. **Other endpoints** 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** 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. 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.

	The Full Analysis Set 3 (FAS3, includes both FAS1 and FAS2) is used for the description of the study population at Baseline. The Safety Set is used for the analyses of the safety variables. The Screened Analysis Set is used for the description of subject disposition. 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. **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. **Primary statistical analysis** For macitentan and ACT-132577 trough concentration analysis, 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 children < 2 y.o. the analysis will be descriptive by age group. 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.

Secondary efficacy endpoints

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 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.

Exploratory endpoints
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.

Safety endpoints
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:

- 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 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:

- 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.

	Cohort of children < 2 y.o. will be summarized separately. **Pharmacokinetic endpoints** 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. 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_{τ}), 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.
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. An Independent Statistical Analysis Center (ISAC) will support the IDMC for their review and recommendation over the entire course of the study. 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. 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.

	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. 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. 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 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 datafrom 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).