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

Clinical Protocol

Protocol Title

A prospective, randomized, double-blind, multicenter, placebo-controlled, parallel group, adaptive Phase 3 study with open-label extension to evaluate efficacy and safety of macitentan 75 mg in inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension.

Macitentan in inoperAble or persistent/reCurrent chronIc ThromboEmbolic Pulmonary Hypertension (MACiTEPH)

Protocol 67896062CTP3001 (Amendment 4); Phase 3

JNJ-67896062 / ACT-064992 macitentan

*Actelion Pharmaceuticals Ltd ("Actelion") is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Actelion studies may vary, such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s):
IND: 77258
EudraCT NUMBER: 2019-004131-24

Status:	Approved
Date:	16 December 2020
Prepared by:	Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-RIM-265157, 5.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4, Version 6	16-Dec-2020
Amendment 3, Version 5	05-Aug-2020
Amendment 2, Version 4	13-Jul-2020
Amendment 1, Version 3	22-Apr-2020
Original Protocol Version 2 (issued)	20-Jan-2020
Original Protocol Version 1	19-Dec-2019

A Protocol Amendment Summary of Changes Table for the current amendment is provided below:

Amendment 4 (16-December-2020)

Overall Rationale for the Amendment: The overall reason for this protocol amendment is to modify the study design for increasing the double-blind (DB) follow-up time. This increase in the DB follow-up time improves the statistical power for the key secondary endpoint (time to clinical worsening). Also, a new substudy is added to provide additional safety data of chronic treatment with macitentan on testicular function in patients with PAH or CTEPH. Specific requirements for Japanese sites were added. Minor corrections and editorial revisions are also being implemented.

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

Section number and Name	**Description of Change**	**Brief Rationale**
Title Page	Legal name of the organization is clarified.	Logistical update
1.1 Synopsis	Changes made to main body text were reflected in the corresponding sections of Section 1.1.	To align the content of synopsis and main body.
1.2 Schedule of Activities (SoA); 4.1 Overall Design; 6.1 Study Intervention (s) Administered	• Details about components of maintenance phase were updated. • Minimum duration of the (DB) period for an individual participant is revised as 28 weeks. • Post-treatment observation period (PTOP) was revised to up to Week 28 (earlier Week 52).	To modify the study design to increase double-blind follow-up time.
1.2 Schedule of Activities (SoA)-Table 1, Table 2, Table 3	Tables were updated for following details: Table 1 (Schedule of Activities (SoA)): • Maintenance phase was divided into fixed duration and variable duration parts. • Revised electrocardiogram (ECG) schedule. • Revised liver function test (LFT) schedule to monthly until Week 52 and every 12 weeks thereafter. • Right heart catheterization (RHC) substudy row was shifted to end under the heading '**Optional Substudies'**	To align with modified study design.

	• Addition of optional male reproductive system safety substudy. • Footnote '9' corresponding to periodic aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) monitoring. was updated and Japan-specific requirements during monthly LFTs were added. • Footnote '13' was revised to indicate that RHC sub-study is mandatory for all Japanese participants based on an agreement with Pharmaceuticals and Medical Devices Agency (PMDA). **Table 2 (Visit and assessment schedule during the open-label extension period):** • Revised ECG assessment schedule to match the ECG schedule during the OL Maintenance Phase. • Deletion of EQ-5D-5L©, PAH-SYMPACT®, PHQ-8, WPAI, and SF36® v2 Acute. • Addition of optional male reproductive system safety sub-study. • Footnotes 1, 3, and 5 were revised. • A new footnote 7 was added to obtain information about vital status and hospitalization via phone calls. **Table 3 (Visit and assessment schedule for participants entering the post-treatment observation period (PTOP)):** • Footnote 5 was revised. • A new footnote 6 was added to clarify that PTOP 7 and 8 visits are not applicable to current protocol version 6 and participants who consented to an earlier version of the protocol will be given the choice to maintain the previous visit schedule and enter the OL period at Week 52. PTOP 7 and 8 visits may still be performed for such participants if they prematurely discontinued study intervention.	
1.3 Schema	Figures 1 and 2 were revised.	To align with modified study design.
2.1 Study Rationale; 6.5 Concomitant Therapy	The word 'inhaled' associated with prostacyclins/ prostacyclin analogs was deleted.	To clarify that inhaled prostacyclins/ prostacyclin analogs will now be allowed as background pulmonary

		hypertension (PH)-specific therapy.
2.2 Background	Results of the recently completed Part A of study 67896062PAH1003 (Effect of macitentan 75 mg on pharmacokinetics [PK] of riociguat and sildenafil in healthy subjects) were added.	The results of this study provide justification for allowing co-administration of macitentan with riociguat or sildenafil.
3 Objectives and Endpoints; 6.1 Study Interventions (s) Administered; 9.4.2.1 Time to first clinical worsening up to EODBT; 10.18 Appendix 18: COVID-19 Appendix (Study visits)	The wording of the secondary objective and the corresponding endpoint of DB treatment period was revised. Secondary objective pertaining to time to clinical worsening was revised as '**up to End-of-double-blind treatment (EODBT)**' from earlier 'up to Week 52'.	DB treatment will no longer end at Week 52 for all participants. For an individual participant, EODBT will occur when the last participant completed Week 28 or as soon as a Clinical Event Committee (CEC)-confirmed clinical worsening event occurred during the variable duration part of the DB period.
3 Objectives and Endpoints: Double-blind treatment period-Secondary; Open-label treatment extension period-Exploratory; 8.2.3 Clinical worsening	• The definition of clinical worsening was revised by removing the below component: '~~Initiation or dose escalation of PH-specific therapy due to worsening of PH based on additional assessments performed at the discretion of the investigator and confirmed by the CEC~~' • A new heading was added to the criteria denoting PH-related deterioration: '**PH-related deterioration from baseline identified by at least one of the following:**' Two notes were added: For CEC-confirmed CW up to EODBT8*: *** Including events occurring up to 7 days after last dose of DB study intervention.** For All-cause death**: ****Including deaths occurring within 30 days of last dose of study intervention caused by an AE that occurs within 7 days of intake of last dose of DB study intervention.**	Initiation and dose escalation of PH-specific therapy is difficult to measure objectively and was therefore removed from the definition of clinical worsening following a recommendation from European Medicines Agency (EMA) Scientific advice. In addition, the heading 'PH-related deterioration identified by' was added to emphasize the specific criteria for identifying a PH-related deterioration as a clinical worsening event. For clarification.
3 Objectives and Endpoints: Double-blind treatment period- Exploratory; Open-label treatment extension period-Exploratory efficacy	• A new exploratory objective (to evaluate the effect of macitentan 75 mg on PH-related deaths and hospitalizations) and corresponding endpoint to evaluate time to first occurrence of CEC-confirmed PH-related death or unplanned PH-related	To evaluate effect of macitentan on hard components (ie., PH-related deaths and hospitalizations of the key secondary endpoint.

	hospitalization up to 7 days after the last dose of DB study intervention were added. • Apart from hospitalizations related to PH worsening, all-cause hospitalizations were included • A new exploratory objective (to evaluate the effect of macitentan 75 mg on low risk criteria and non-invasive risk group defined from WHO FC, 6MWD and NT-proBNP thresholds) and the corresponding endpoints were updated.	To assess the effect of macitentan on hospitalizations up to EODBT. To evaluate the effect of macitentan 75 mg on low risk criteria and non-invasive risk group.
3 Objectives and Endpoints; 8.6.3 Pharmacokinetic Parameters and Evaluations; 9.4.3 Safety Analyses; 9.4.4 Other Analyses	The term 'Intervention-emergent' was replaced with 'Treatment-emergent' in endpoints corresponding to safety objectives.	For wording consistency throughout the document.
3 Objectives and Endpoints: OL treatment extension period-Exploratory efficacy	Two exploratory objectives and corresponding endpoints were added.	To evaluate effect of macitentan 75 mg on PH-related deaths and hospitalizations and overall survival and hospitalizations.
4.1 Overall Design	An optional male reproductive system safety sub-study was added.	To provide additional safety data of chronic treatment with macitentan on testicular function in patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH), as requested by EMA Scientific advice.
4.1 Overall Design	• Detailed information about duration of the DB treatment period was added, keeping the sample size unchanged (n=144) as a possible outcome of the interim analysis. • Eligibility criteria for participants who completed PTOP up to Week 28 to enter the open-label (OL) extension period were specified. • Duration of the DB period was revised as minimum 28 weeks and maximum approximately 3.5 years. • After completion of the DB treatment period, eligible participants will enter the OL treatment period**, which will last until 2 years after the last participant completed the fixed duration part of the DB period**.	To describe the changes to the study periods triggered by the revised study design.
4.2 Scientific Rationale for Study Design	Following text was modified: 'Participants who are on **Riociguat,** PDE-5 inhibitors or oral or SC prostanoids at	To allow participants with riociguat background therapy based on results of drug-drug interaction (DDI) study.

	baseline are allowed to remain on these medications.' ~~Riociguat will be allowed as background therapy once absence of a clinically meaningful DDI interaction has been confirmed in a separate study~~.	
	A new measure to minimize the risks of prolonged DB treatment for the participants was added as follows: '**After Week 28 (timepoint of assessing the primary endpoint), transition to OL macitentan 75 mg is possible in case of a CEC-confirmed clinical worsening event.**'	The possibility of crossing-over to OL study intervention in case of a CEC-confirmed clinical worsening event after Week 28 ensures that participants have access to active treatment when they need it.
	Rationale for implementing a DB period of variable duration was added and rationale for the OL extension period was updated to state that the **earliest possible timepoint of entering the OL extension is Week 28**.	To provide justification for revised study design.
4.4 End of Study Definition	• Table 4 (EOS visits definition) was deleted and status of participants were specified to aid in defining EOS visit for an individual participant. • Definition of study completion was revised. • Definition of completion of OL Treatment Extension period was revised.	Content of the section updated based on revised study design.
5.1 Inclusion Criteria	Updated a reference to criteria for inclusion in the male reproductive system safety (spermatogenesis) sub-study (Appendix 17).	To update information about new optional sub-study
5.1.1 Inclusion Criteria for OL extension period	Inclusion criteria for OL extension period were deleted.	To rearrange the information in Section 5.3.
5.2 Exclusion Criteria	• Exclusion criteria 1 and 2 related to the disease were updated. • Exclusion criterion 5 related to comorbidities was updated. • Exclusion criterion 11 related to macitentan use was updated. • Exclusion criterion 12 related to macitentan use was removed. • Exclusion criterion 13 related to macitentan use was updated. • Exclusion criterion 24 related to general criteria was updated.	Exclusion criteria 2, 5, 13, and 24: Time windows were updated to reflect the revised duration of the DB period. Exclusion criterion 1: The acceptable time window for acute pulmonary embolism (PE) prior to Screening was reduced from 6 to 3 months, since most of the recovery after a true incident PE is expected to happen within 3 months. Exclusion criterion 11 and 13 were revised to allow use of inhaled prostacyclins/prostacyclin analogues, given that oral- and

		subcutaneous routes of administration are allowed. Exclusion criterion 12 was removed since use of riociguat as background therapy is now permitted.
5.3 Qualifying Criteria for Transitioning to the OL Extension	Sections 5.1.1 and 5.2.1 mentioning inclusion and exclusion criteria respectively, to qualify for enrolment in OL extension were deleted and combined under a new Section 5.3. Section 4.1 revised with corresponding update.	To retain the information essential from operational point of view in one common section.
6.1 Study Intervention (s) Administered	• Table 4 was updated to include information about dosage levels during revised maintenance phase. • Following text added: **Extra bottles can be requested via interactive web response system (IWRS) if needed (eg, if a visit cannot be scheduled within the visit window).** • Tables 5 and 6 were updated to include information about revised study intervention dispensation schedule.	To align with revised study design.
6.5 Concomitant Therapy	Soluble guanylate cyclase stimulators (eg, riociguat) and corresponding note deleted from the list of prohibited concomitant medications.	To allow participants with riociguat background therapy based on results of DDI study.
6.5.1 Rescue Medication	Content of this section was revised to permit the use of riociguat as a rescue medication.	To allow rescue treatment with riociguat based on results of DDI study.
6.7 Continued Access to Study Intervention After the End of the Study	• Heading of the section was revised (Earlier- 'Intervention After the End of the Study'). • Information regarding collection of vital status and hospitalization will be collected approximately every 6 months until completion of the study for all participants who had their EOS visit before the completion of the study. Options for post-trial access to study intervention were added.	To align with revised study design.
7.1.1 Permanent Discontinuation	New text updated as follows: **The safety follow-up visit will be waived in case the participant moves to a continued access program and in that case EOLT will be the last visit in the study.**	To clarify that the requirement to have an end of study (EOS) visit 30 days after last intake of study intervention does not apply to participants who will move to a continued access program.
7.1.2 Temporary Discontinuation	The requirement to limit the total allowed study intervention interruption time to 28 days was removed.	To align the requirements for study intervention discontinuation with the revised

	Rules for interrupting and re-introducing study invention when a forbidden medication (except endothelin receptor antagonists [ERAs]) is administered were added.	study design: with the variable duration of the DB treatment period, the need to restrict the allowed interruption time to 28 days does not apply any longer. The need to administer a forbidden medication does not necessarily need to result in permanent treatment discontinuation. Study intervention can be re-started under certain conditions.
7.3 Lost to Follow-up	Information about collection of vital status of the participant was updated.	To align with the standard protocol template language.
8 Study Assessment and Procedures	• Maximum amount of blood drawn from each participant will not exceed **260** mL **per year** (earlier 250 mL). • The range of volume of blood collected during each visit was updated as **15** to **25 mL** (earlier 6.3 to 20 mL). • Volume of blood collected per visit during OL extension period **will not exceed 15 mL** (earlier 6.3 mL). • The amount of blood to be withdrawn for optional sub-study of male reproductive system safety is mentioned in Appendix 17.	To update the volume of blood withdrawn to align with revised study design. To provide information about volume of blood withdrawn in new sub-study.
8.1.1 Eligibility Adjudication procedure	Heading of the section updated from 'Adjudication Procedure' to 'Eligibility Adjudication Procedure'.	To align with Janssen TransCelerate template.
8.1.2 Clinical Events Adjudication Procedure	A new section was added to describe the process for adjudicating clinical worsening events to be eligible to enter the OL extension period.	The revised study design allows transition to OL study intervention in case of a CEC-confirmed clinical worsening event.
8.2.1 6-minute Walk Test	Following text was added: '**If a 6MWT cannot be performed at a scheduled visit beyond Visit 2 or at an unscheduled visit, a reason must be provided (ie, PAH-related or other).**'	To document the reason for not performing the 6MWT at a scheduled visit beyond Visit 2 or at an unscheduled visit.
8.2.3 Clinical Worsening	Following text was added: '**If a repeat 6MWT cannot be performed due to PH-related deterioration, this needs to be documented in the eCRF.**'	To document the related information in electronic case report form (eCRF).
8.2.4 Risk Categories for Clinical Worsening and Death	A new section was added to describe the risk categories. A new Table 8 (An outline of risk stratification strategy) was added.	Number of risk criteria and proportion of participants in each risk category were added as an exploratory endpoint.

8.2.7.1 PAH SYMPACT®	The use of a paper-based PAH-SYMPACT® questionnaire is permitted under exceptional circumstances.	To give participants who are unable to use the mobile device despite adequate training the option to complete the questionnaire on paper. This back-up solution is intended to limit the risk of missing data.
8.2.8 Right Heart Catheterization	• For participants who underwent PEA or BPA, the time between the procedure and the RHC was revised to be at least 12 weeks (earlier 24 weeks). • A new footnote 'a' was added to indicate that RHC substudy is mandatory for all participants enrolled in Japan based on an agreement with Pharmaceuticals and Medical Devices Agency (PMDA).	To align with revises study design. To avoid a local amendment for Japan, the requirement for Japanese sites to include all participants in the substudy was added as a footnote.
8.3.5 Clinical Safety Laboratory Assessments	• AST/ALT monitoring will be performed 3-monthly after 52 weeks exposure in the **DB or** OL period**s, unless continued monthly monitoring is mandated based on local regulatory requirements**. • Updated a requirement for Japanese participants for additional assessments to be conducted on monthly visit for liver function tests and their documentation in source notes and if assessments are related to adverse events (AEs), they must be recorded in eCRF.	For clarification. To update the requirements for Japanese sites.
8.5 Treatment of Overdose	Content of the section was updated to provide information about treatment of overdose to investigator or treating physician.	To align with Janssen TransCelerate template; to align with safety reporting processes.
8.9 Medical Resource Utilization	Medical resource utilization data will include all PH-related events and hospitalizations (CTEPH was updated as PH).	To capture all available information.
9 Statistical Consideration	Details about statistical analysis plans (SAPs) were updated.	To clarify the types of SAPs that will be developed during the course of the study.
9.1 Statistical Hypotheses	• Section of statistical hypotheses was subdivided into Sections 9.1.1 (Primary Hypothesis) and 9.1.2 (Secondary Hypotheses). • Primary end point 'change in 6MWD from baseline to Week 28' was mentioned in the section of primary hypothesis. • The new section of secondary hypotheses was also updated with	To provide clarification on the *a priory* order of hypothesis testing for secondary endpoints.

	Table 9 (Secondary endpoints and associated hypotheses).	
9.1.3 Overall Testing Strategy	A new Section 9.1.3 was added to include information about overall testing strategy.	For clarification.
9.2 Sample Size Determination	• A new subsection 9.2.1 (Estimated Power for Key Secondary Endpoint: Time to Clinical Worsening) was added. • A new table (Table 10) was included to provide information about expected clinical worsening (CW) events and associated power.	To provide information on increased power for the key secondary endpoint time to clinical worsening (TTCW) due to revised study design.
9.3 Populations for Analyses	• Table 11 and 12 were updated for pharmacokinetic/pharmacodynamic (PK/PD) and patient reported outcome (PRO) analysis sets and corresponding timepoints to include new information. • A new analysis timepoint was updated in text as follow: '**Interim analysis of OL extension period: Timing is determined by the data cutoff date of the final analysis (DB period).**	• For consistency with the SAP. • To clarify that an IA will be performed using data from DB period and OL period at the time of DB final analysis.
9.4 Statistical Analyses	• SAP-Part 1 and 2 details were updated. • Information about unblinded interim analysis (IA) and control for type I error inflation was included. • Supporting literature publications were updated in Section 11.	• For clarification. • Previous version of the protocol indicated that the details on type I error control due to unblinded SSRE will be provided in the SAP. However, to address a question from an Ethics Committee (EC), these details are now added to the protocol.
9.4.1 primary Efficacy Analysis	• Population-related estimand describing attribute was revised as: '**Participants diagnosed with CTEPH, meeting the study eligibility criteria**'. • Content of intercurrent events (IEs) was revised to clarify about the applicable imputation rules. • Content corresponding to Handling of missing data, Main analysis and Sensitivity analyses was updated. • Table 13 was updated to include above-mentioned changes.	Minor modifications to clarify estimand population, imputation rules and handling of implausible values.
9.4.2 Secondary Efficacy Endpoint Analyses	• Section was revised to include information about combination tests	Previous version of the protocol indicated that the details will be

	which will be applied to each of the secondary efficacy endpoints in order to account for type I error inflation due to unblinded sample size re-estimation (SSRE).	provided in the SAP. To address a question from an (EC), this information is now added to the protocol.
9.4.2.1 Time to first clinical worsening up to EODBT	• Population related estimand describing attribute was revised as: '**Participants diagnosed with CTEPH, meeting the study eligibility criteria**'. • Content of the section was updated to align with revised study design. • Supportive exploratory/sensitivity analyses were updated.	• For alignment due to revised study design. • Minor clarifications to some details of the previously planned analyses.
9.4.2.2 Improvement in WHO FC from baseline to last value while on treatment up to Week 28 (yes/no); 9.4.2.3 Change from baseline to last value while on treatment up to Week 28 in PAH-SYMPACT®; 9.4.2.5 Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity	Imputation rules were updated for IEs corresponding to premature discontinuation/administration of rescue therapy.	Minor modification to clarify imputation rules.
9.4.4 Other Analyses: Exploratory Analyses	Following statement was added: '**Descriptive /sensitivity analyses will be performed to evaluate the impact of COVID-19 pandemic on the efficacy and safety endpoints. Details will be provided in the SAP-Part 1.**'	For clarification.
9.4.5 Interim Analysis	Section was updated to include further details of the IA-SAP.	Minor modifications based on the Independent Data Monitoring Committee (IDMC) charter for clarification.
10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Information regarding provision of a case narrative or other relevant information to CEC was updated.	For clarification.
10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Information regarding Product Quality Complaint (PQC) Handling was updated.	To align with Janssen TransCelerate Template.
10.5 Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	• Table of 'Acceptable methods of contraception' was updated: Intrauterine devices (IUDs) and implantable hormonal contraceptives moved to option 1 (standalone methods) and following text was added: '**If a hormonal contraceptive is chosen, it must be taken for at least 28 days prior to randomization**'. • Information regarding use of consistent and approved contraceptive	To align with the contraceptive requirements of the Janssen TransCelerate template To provide information about

	methods per local regulations was updated and table footnote revised. A new footnote is added to indicate contraceptive methods approved in Japan.	approved contraception methods.
10.7 Appendix 7: Sponsor 6-minute Walk Test Guidance	Heading of the section was updated (earlier: Appendix 7: Actelion 6-minute walk test guidance).	To align with Janssen TransCelerate template.
10.8 Appendix 8: Borg CR10 Scale®	A new footnote 'a' was added: 'The instructions for rating dyspnea have been customized by the sponsor based on the instructions for rating exertion. These modifications have not been validated by Borg Perception AB.'	For clarification.
10.11 Appendix 11: 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L©)	A new image for EQ-5D-5L© visual analog scale (VAS) scale was added.	To provide additional information.
10.17 Appendix 17: Guidance on Male Reproductive System Safety Sub-study	A new appendix was added to provide information about background, design, rationale, objectives and endpoints, population, assessments and analyses. Corresponding references were updated in Section 11.	To provide requisite information for conduct of male reproductive system safety sub-study.
10.18 Appendix 18: Study Conduct During a Natural Disaster	Section was renumbered and heading of the section was revised to 'Study Conduct During a Natural Disaster' (earlier: COVID-19 Appendix)	To align with Janssen TransCelerate template.
Throughout the protocol	• Interactive randomization system (IRS) updated to IWRS. • New abbreviations were updated in Section 10.1. • Minor corrections and editorial revisions were made.	For clarity and consistency; minor errors were noted.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

A prospective, randomized, double-blind, multicenter, placebo-controlled, parallel group, adaptive Phase 3 study with open-label extension to evaluate efficacy and safety of macitentan 75 mg in inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension.

Macitentan in inoperAble or persistent/reCurrent chronIc ThromboEmbolic Pulmonary Hypertension (MACiTEPH)

Macitentan (ACT-064992, Opsumit®) is an orally active, non-peptide, potent dual endothelin receptor (ET_A and ET_B) antagonist (ERA) approved at a dose of 10 mg for the treatment of pulmonary arterial hypertension (PAH). Macitentan offers a new mode of action for the treatment of inoperable and persistent/recurrent CTEPH and addresses an important unmet medical need for an alternative treatment in this indication. MACiTEPH will assess the role of macitentan as a first-line, as well as an add-on treatment for CTEPH population.

OBJECTIVES AND ENDPOINTS

Double-blind treatment period	
Objectives	**Endpoints**
Primary	
To evaluate the effect of macitentan 75 mg versus placebo on exercise capacity at Week 28 in participants with chronic thromboembolic pulmonary hypertension (CTEPH).	Change from baseline to Week 28 in exercise capacity (6-minute walk distance [6MWD], as measured by the 6-minute walk test [6MWT]).
Secondary	
To evaluate the effect of macitentan 75 mg versus placebo on time to clinical worsening up to EODBT.	Time to first Clinical event committee (CEC) confirmed clinical worsening up to EODBT*. Clinical worsening is defined as the occurrence of at least one of the following events: – All-cause death** – Heart and/or lung transplantation – Unplanned pulmonary hypertension (PH)-related hospitalization – PH-related deterioration from baseline identified by at least one of the following: – Persistent[a] increase in World Health Organization functional class (WHO FC) that cannot be explained by another cause (eg, viral infection) – Persistent[a] deterioration by at least 15% in exercise capacity, as measured by the 6MWD – New or worsening signs or symptoms of right heart failure – Rescue pulmonary endarterectomy (PEA) and/or balloon pulmonary angioplasty (BPA) procedure due to worsening of PH. * Including events occurring up to 7 days after last dose of DB study intervention

	**Including deaths occurring within 30 days of last dose of study intervention caused by an AE that occurs within 7 days of intake of last dose of DB study intervention. [a] Confirmed by a second measurement performed on a different day within 2 weeks
To evaluate the effect of macitentan 75 mg versus placebo on WHO FC at Week 28.	Improvement in WHO FC from baseline to Week 28 (yes/no).
To evaluate the effect of macitentan 75 mg versus placebo on quality of life at Week 28	Change from baseline to Week 28 in • Pulmonary Arterial Hypertension – Symptoms and Impact (PAH-SYMPACT®) o Cardiopulmonary symptom domain score o Cardiovascular symptom domain score • Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L©) utility score.
To evaluate the effect of macitentan 75 mg on daily physical activity	Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity.
Safety	
• To evaluate the safety and tolerability of macitentan 75 mg in participants with CTEPH.	• All-cause death up to 30 days after study intervention discontinuation • Treatment-emergent adverse events (AEs) up to 30 days after study intervention discontinuation • AEs leading to premature discontinuation of study intervention • Treatment-emergent AEs of special interest (AESI) up to 30 days after study intervention discontinuation • Treatment-emergent serious adverse events (SAEs) up to 30 days after study intervention discontinuation • Treatment-emergent ECG abnormalities up to 30 days after study intervention discontinuation • Treatment-emergent marked laboratory abnormalities up to 30 days after study intervention discontinuation • Change in laboratory variables from baseline to all assessed timepoints during the study • Change in vital signs (diastolic blood pressure [DBP], systolic blood pressure [SBP], and pulse rate [PR]) and body weight from baseline to all assessed timepoints during the study

Open-label treatment extension period	
Objectives	**Endpoints**
Efficacy	
To evaluate the long-term effect of macitentan 75 mg on overall survival and hospitalizations.	• All-cause death • All-cause hospitalization
Safety	
To evaluate the long-term safety and tolerability of macitentan 75 mg in participants with CTEPH.	• All-cause death up to 30 days after study intervention discontinuation • Treatment-emergent AEs up to 30 days after study intervention discontinuation • Treatment-emergent AESI up to 30 days after study intervention discontinuation

	• AEs leading to premature discontinuation of study intervention • Treatment-emergent SAEs up to 30 days after study intervention discontinuation • Treatment-emergent marked laboratory abnormalities up to 30 days after study intervention discontinuation • Change in laboratory variables from baseline to all assessed timepoints • Change in vital signs (DBP, SBP, and PR) and body weight from baseline to all assessed timepoints

Hypothesis

The null and alternative hypotheses are formulated in terms of the difference between intervention groups at Week 28, as estimated from a Mixed Model Repeated Measures (MMRM) approach utilizing all post-baseline values (Weeks 4, 8, 12, 16, 20, 24 and 28) of 6MWD changes from baseline.

OVERALL DESIGN

This is a randomized, double-blind (DB), placebo-controlled, multicenter, two-stage, group sequential, adaptive study of macitentan 75 mg in men and women between 18 and 80 years of age, with a diagnosis of inoperable or persistent/recurrent CTEPH.

The study includes 2 optional sub-studies:

- A hemodynamic sub-study which will be conducted at centers that are able to comply with study-specific RHC guidelines (Appendix 16)

- A male reproductive system safety sub-study which will be conducted in centers having access to adequate facilities. The aim of the sub-study is to provide additional safety data of chronic treatment with macitentan on testicular function in patients with PAH or CTEPH, and it will thus be offered to male patients participating in MACiTEPH or UNISUS (AC-055-315; macitentan 75 mg in PAH). The data from this sub-study will be pooled with the data from UNISUS and analyzed independently (ie., it will not be included in the MACiTEPH CSR). (Appendix 17)

NUMBER OF PARTICIPANTS

At least 144 participants will be randomized in a 1:1 ratio to macitentan 75 mg or placebo.

INTERVENTION GROUPS AND DURATION

The study comprises the following periods:

- A screening period of at least 14- and up to 60 days
- A DB treatment period, which starts on Day 1 (Randomization, baseline) and ends on the day of last DB study intervention intake. The DB period consists of an 8-week uptitration phase and a maintenance phase. The maintenance phase is divided into a fixed duration part, at the end of which the primary endpoint is assessed, and a variable duration part. Participants will remain on DB treatment until the all participants have completed the 28-week fixed duration part, or until

they experience a CEC-confirmed clinical worsening event and transitioning to OL macitentan 75 mg is considered to be in the participant's best interest. The minimum duration of the DB period for an individual participant is 28 weeks.

- A post-treatment observation period (PTOP) up to Week 28 for participants who prematurely discontinue DB study intervention but do not withdraw consent.
- An open-label (OL) extension period, which starts on the day of the EODBT visit and ends with the 'End of open-label treatment' (EOLT) visit. The OL extension period will end 104 weeks after the last participant has completed the DB treatment period.
- A safety follow-up period, which starts on the day after the last dose of study intervention and ends with a post-treatment safety follow-up visit (30 [+5] days thereafter, to collect any AEs since the last study visit).

The entire study is expected to last approximately 6 years.

Description of Interventions

An overview of the doses of macitentan and matching placebo is shown below:

Study intervention name:	Macitentan	Placebo
Dose formulation	Film-coated tablets and matching placebo	
Unit dose strength(s)	10 mg 37.5 mg 75 mg	Placebo
Dosage levels	**Double-blind treatment period:** **Titration (8 weeks)** Day 1 to Week 4 (day before visit): 10 mg od or matching placebo Week 4 to Week 8 (day before visit): 37.5 mg od or matching placebo **Maintenance:** Fixed duration part: Week 8 to Week 28 (day before the visit): 75 mg od or matching placebo Variable duration part: Week 28 to EODBT of last participant or CEC-confirmed CW event of the individual participant, whichever occurs first.: 75 mg od or matching placebo **Open label extension period** **Double-dummy uptitration (8 weeks)**: Ex-placebo arm: Day 1 to Week 4 (day before visit): 10 mg tablet + Placebo-matching 75 mg tablet Week 4 to Week 8 (day before visit): 37.5 mg tablet + Placebo matching 75 mg tablet Ex-macitentan arm: Day 1 to Week 4 (day before visit): 75 mg tablet + Placebo-matching 10 mg tablet Week 4 to Week 8 (day before visit): 75 mg tablet + Placebo-matching 37.5 mg tablet **Maintenance:** Week 8 to EOLT: 75 mg od	
Route of administration	Oral	
Dosing instructions	**Study intervention administration:** One tablet once a day, preferably in the morning.	
Packaging and labeling	Study intervention will be provided in childproof bottles containing 36 tablets each.	

	Each bottle will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the bottle.

CEC = clinical event committee; CW = clinical worsening; EODBT = end of double-blind treatment; EOLT = end of open-label treatment.

No dose modification is allowed during the course of the study for the study intervention. Study treatment must be interrupted or permanently discontinued if any of the criteria described in Section 7.1 are met. For details on rescue medication, refer to Section 6.5.1.

EFFICACY EVALUATIONS

Key efficacy assessments include 6MWD and clinical worsening, as well as WHO FC, the PAH SYMPACT® and EQ-5D-5L© questionnaires and accelerometry.

SAFETY EVALUATIONS

Key safety assessments will include the monitoring of AEs, physical examinations, measurement of body weight, vital signs measurements, pulmonary function tests, electrocardiograms and clinical laboratory tests.

STATISTICAL METHODS

Sample size calculation

Sample size determination relies on the following assumptions:

- Targeted treatment effect (difference in changes from baseline to Week 28) = 33 m,
- Common standard deviation of change from baseline to Week 28 = 70 m

Under these assumptions, a fixed sample size of 2 × 72 participants has a power of 80% using a one-sided type I error rate of 2.5% (based on an ANOVA model without interim analysis).

This study implements an adaptive group sequential design with one interim analysis (see Section 9.4.5) to reassess the required sample size to maintain study power as well as to potentially prematurely stop the study for futility. A maximum of 230 participants is considered for this study based on practical considerations.

Incorporating the interim analysis and above adaptations, the global power is 89% (based on an ANOVA model).

Statistical Hypotheses

The null and alternative hypotheses are formulated in terms of the difference between intervention groups at Week 28, as estimated from an MMRM.

If $\mu_{MACI,28}$ and $\mu_{PBO,28}$ denote the mean changes from baseline in 6MWD at Week 28 for the participants treated with macitentan and placebo, respectively, then the following hypotheses can be considered:

$$H0: \Delta = \mu_{MACI,28} - \mu_{PBO,28} \leq 0$$
$$H1: \Delta = \mu_{MACI,28} - \mu_{PBO,28} > 0$$

The null hypothesis will be tested at a study-wise 1-sided significance level of 0.025.

The MMRM used for the primary analysis is specified in Section 9.4.1.

Primary Efficacy Analysis

The primary efficacy endpoint is change in 6MWD from baseline to Week 28.

Estimand

The estimand is described according to the following four attributes:

A. Population: Participants diagnosed with CTEPH meeting the study eligibility criteria.

B. Variable: 6MWD changes from baseline at Weeks 4, 8, 12, 16, 20, 24 and 28.

C. Intercurrent events:

The following intercurrent events (IE) are considered:

- **Death**: A composite strategy will be used for deaths occurring up to 7 days after study intervention discontinuation without administration of rescue CTEPH therapy. All scheduled assessments following the date of death will be replaced by a 'worst-case' imputation, ie, the sum of the participant's baseline value and the lowest observed value of 6MWD change from baseline across both treatment groups and over all assessments up to Week 28. All assessments prior to the death, as well as all imputed assessments, thereafter, will be considered in the analysis
- **Premature discontinuation/Administration of rescue therapy**: A composite strategy will be employed for premature discontinuation of study intervention that are possibly treatment related (eg, clinical worsening, lack of response, adverse events, informed consent withdrawal due to tolerability issues) and/or administration of rescue CTEPH therapy (ie, associated. PH-specific therapy, PEA and/or BPA procedures). All 6MWD assessments performed after end of intervention (possibly treatment related) plus 7 days or after administration of rescue therapy will be ignored in the analysis and for each visit occurring after the IE, participant's baseline 6MWD value plus the minimum of the following values: (1) the last observed value (observed 6MWD change from baseline) prior to intercurrent event at the participant level and (2) the 25^{th} percentile of observed 6MWD change from baseline values (both treatment groups pooled and over all assessments up to Week 28), will be considered instead.

D. Population-level summary:

Difference in mean 6MWD change from baseline at Week 28 between macitentan and placebo as estimated from the MMRM in the Full analysis set (FAS; as randomized).

Statistical model

The model will include treatment (via an indicator variable for randomized intervention), time (via a categorical variable for visit), treatment-by-time interaction, one indicator variable for each stratification factor as fixed effects and baseline 6MWD as a covariable. An unstructured variance-covariance matrix will initially be specified. If convergence issues arise from the latter, a heterogeneous first-order autogressive (ARH(1)) covariance structure will be considered.

Main analysis

The main analysis refers to the primary analysis performed when all participants have completed the 28-week DB period or prematurely discontinued the study. This analysis will be performed on the

FAS. The treatment effect (Δ) estimate, as well as the associated p-value for the statistical hypothesis of interest will be obtained from the MMRM and the latter will be compared to the nominal 1-sided type I error of 0.025 (See Section 9.4.1 for details).

In addition, the treatment effect will be estimated at 4-weekly intervals from baseline to Week 28 based on the same model along with their associated 95% CIs.

Secondary Efficacy Analysis

- **Time to first clinical worsening up to EODBT**

The first secondary efficacy endpoint is time to clinical worsening up to EODBT (See definition in Section 9.4.2.1).

Analysis

A log-rank test stratified by intervention group and randomization stratification factors will be performed in the FAS. The resulting 1-sided p-value will be provided and compared to the nominal 1-sided type I error of 0.025.

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

- **Improvement in WHO FC from baseline to last value while on treatment up to Week 28 (yes/no)**

Improvement (decrease) in WHO FC from baseline to Week 28 will be calculated for each participant.

Analysis

The data in the FAS will be analyzed by a Cochran-Mantel-Haenszel test adjusted by WHO FC at baseline, intervention group, and randomization stratification factors. The resulting p-value will be compared to the nominal 1-sided type I error of 0.025.

- **Change from baseline to last value while on treatment up to Week 28 in PAH-SYMPACT®**

The change from baseline to last value while on treatment up to Week 28 will be calculated for each participant and for each domain (cardiopulmonary symptoms and cardiovascular symptom). Separate tests will be conducted for each domain according to the above hierarchical order.

Analysis

The change from baseline to last value while on treatment up to Week 28 will be analyzed by means of non-parametric Mann-Whitney U test in the FAS. A point estimate for the placebo corrected location shift will be displayed along with associated 95% CI and p-value using the Hodges-Lehmann method. The resulting p-value from the U statistic will be compared to the nominal 1-sided type I error of 0.025.

- **Change from baseline to last value while on treatment up to Week 28 in EQ-5D-5L© utility score**

Endpoint definition

The change from baseline to last value while on treatment up to Week 28 will be calculated for each participant. Utilities will be calculated according to the crosswalk algorithm developed by the EuroQoL group (Van Hout 2012) in order to follow the NICE position paper (NICE 2018), ie, EQ-5D-5L© values will be mapped into the 3L values for analysis.

Analysis

The analysis will follow the same principles as for the PAH-SYMPACT® in the FAS.

- **Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity**

Endpoint definition

For each scheduled visit, the 14 days prior to the visit will be considered as the assessment period for physical activity.

At each visit, the proportion of time spent in moderate to vigorous activity will be estimated.

Analysis

The data in the FAS will be analyzed by an ANCOVA adjusting for baseline actigraphy value and randomization stratification factors. The resulting p-value will be compared to the nominal 1-sided type I error of 0.025.

Safety Analysis

All safety analyses will be made on the Safety Population.

Adverse Events

Treatment-emergent adverse events are AEs with onset during the intervention period or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint by intervention group. Frequency tabulations of the abnormalities will be made.

Vital signs

Descriptive statistics of pulse rate, SBP and DBP values and changes from baseline will be summarized at each scheduled timepoint by intervention group.

1.2 Schedule of Activities (SoA)

Table 1: Schedule of Activities (SoA)

PERIOD	Name	SCREENING	DOUBLE-BLIND TREATMENT PERIOD											Unscheduled[1]	Safety follow-up
PHASE	Name		Up-titration Phase			Maintenance Phase 75 mg									
			10 mg	37.5 mg			Fixed duration part						Variable duration part		
VISITS	Number/ Name	1	2	3	4☎	5	6	7 ☎	8	9	10-12	13	14-X	EODBT[2]	Anytime in case of clinical worsening
	Timing	At least 14 and up to 60 days prior to D1[1]	D1 / Randomization	W 4 (±3 d)	W 5 (±3 d)	W 6 (±3 d)	W 8 (±3 d)	W 9 (±3 d)	W10 (±3 d)	W12 (±3 d)	W16/20/24 (±5 d)	W 28 (±5 d)	W 40, every 12 weeks thereafter (±5d)	End of DB treatment (±5 d)	30 (+ 5) days after study interv. Disc.
Screening/Administrative															
Informed Consent (ICF)[3]		X													
Eligibility		X													
Demographics		X													
Medical history		X													
RHC (historical allowed[4])		X													
V/Q scan, PA, CTPA, MRA[5]		X													
PFTs[6]		X													
DB Study interv. Dispensing			X	X			X			X	X	X	X		
Safety assessments															
Physical examination[7]		X	X	X		X	X		X	X	X	X	X	X	X
Vital signs (BP, PR)		X	X	X		X	X		X	X	X	X	X	X	X
Body weight		X	X	X		X	X		X	X	X	X	X	X	X
Home body weight monitoring			At least once per week until Week 12												
12-lead ECG			X				X			X		X	W 52		
Clinical Laboratory tests															
Central laboratory test		X	X	X		X	X		X	X	X	X	X	X	X
Serum pregnancy test[8]		X	X	X			X			X	X	X	X	X	X
Liver function tests		X	X	X		X	X		X	X	X	Monthly until W 52, every 12 weeks thereafter[9]			X
Urine pregnancy test[10]			X									Monthly in between visits starting at Week 32			
Efficacy assessments															
6MWT / BDI		X	X	X			X			X	X	X	X	X	X
Accelerometry[11]		Daily during waking hours													
WHO FC		X	X	X		X	X		X	X	X	X	X	X	X
Clinical worsening			X	X		X	X		X	X	X	X	X	X	X
EQ-5D-5L©			X	X			X			X	X	X	Week 40, 52		
PAH-SYMPACT™		(X[12])	X	X			X			X	X	X	Week 40, 52		
PHQ-8, WPAI, SF36 v2			X	X			X				W 16	X	Week 52		
PGA-S			X	X			X				W 16	X	Week 52		
Ongoing participant review															
Concomitant therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs/AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X

PERIOD	Name	SCREENING	DOUBLE-BLIND TREATMENT PERIOD											Unscheduled[1]	Safety follow-up
PHASE	Name		Up-titration Phase				Maintenance Phase 75 mg								
			10 mg	37.5 mg			Fixed duration part						Variable duration part		
VISITS	Number/ Name	1	2	3	4☎	5	6	7 ☎	8	9	10-12	13	14-X	EODBT[2]	Anytime in case of clinical worsening	
	Timing	At least 14 and up to 60 days prior to D1[1]	D1 / Randomization	W 4 (±3 d)	W 5 (±3 d)	W 6 (±3 d)	W 8 (±3 d)	W 9 (±3 d)	W10 (±3 d)	W12 (±3 d)	W16/20/24 (±5 d)	W 28 (±5 d)	W 40, every 12 weeks thereafter (±5d)	End of DB treatment (±5 d)		30 (+ 5) days after study interv. Disc.
Pharmacokinetics / Pharmacodynamics																
PK samples[13]			X	X			X			X		X				
ET-1 samples[13]			X	X			X			X		X				
NT-proBNP			X	X			X			X	X	X	X	X	X	
Research biomarker			X	X			X			X		X		X		
Optional Substudies																
RHC [14]		X										X				
Male reproductive system safety sub-study		Please refer to the schedule of assessments in Appendix 17, Section 4.														

Footnotes:

[1] During the double-blind period, an unscheduled visit must be performed in case of a suspected clinical worsening or initiation/dose escalation of PH-specific therapy. The assessments performed at the unscheduled visit include, but are not limited to concomitant therapy, physical examination, vital signs (BP/PR) weight, laboratory assessment, post-dose 6MWT/Borg CR10 Scale® and WHO FC.

[2] In case of premature discontinuation of double-blind study intervention, the EODBT visit must be performed within 7 days of taking the decision to stop study intervention. If the premature EODBT visit falls within the time window of a regular scheduled visit, then the visits can be combined, and all assessments pertaining to these visits will be performed.

[3] Must be signed before first study-related activity.

[4] If historical RHC data from the 24-week period prior to Randomization are available, these can be used. Otherwise, the RHC needs to be repeated at Screening.

[5] Confirmation of diagnosis and inoperability of CTEPH based at least 2 of these assessments performed in the 14-month period prior to Randomization. Confirmation of diagnosis of persistent recurrent CTEPH after BPA based on at least one of these assessments in the 14-month period prior to Randomization.

[6] Historical PFTs accepted if performed within 12 months prior to Screening and judged reliable by the investigator, provided the participant's pulmonary status remained unchanged during this time. Only necessary for participants with a known or suspected history of significant lung disease.

[7] Physical examination at Screening will include assessment of the Child Pugh score for participants with known hepatic impairment.

[8] For women of childbearing potential. Additional serum pregnancy test to be performed in case of a positive urine pregnancy test.

[9] Monthly AST/ALT monitoring required until Week 52. Thereafter, AST/ALT monitoring can be performed every 12 weeks, unless continued monthly monitoring is mandated based on local regulatory requirements. Local laboratory can be used. If study treatment is interrupted/discontinued due to AST/ALT elevations, weekly tests are to be performed until to the values return to pre-treatment levels or within normal ranges. *Requirement for Japan:* Monthly AST/ALT monitoring is required. Whenever participants have monthly liver function tests, the following assessments should be conducted and reported in source notes: physical examination, body weight, blood pressure/pulse rate, and hematology (hemoglobin, hematocrit, and RBC count). These assessments must be recorded in the eCRF only if they are related to AEs.

[10] Women of childbearing potential only. To be performed monthly (at site or at home if the interval between 2 regular site visit exceeds 4 weeks).

[11] The accelerometer will be provided to the participant at Screening, and worn daily during waking hours up to Week 28.

[12] The participant will receive the mobile device at Screening and will be trained on its use. Completion of the PAH-SYMPACT® will start 7 days prior to Visit 2 (Randomization).
[13] PK and ET-1 samples to be drawn pre-dose and 2-10 hours post-dose.
[14] Participation in RHC sub-study is optional, except for Japan, where the participation in the sub-study is mandatory based on an agreement with PMDA. A historical RHC performed within 60 days of Randomization can be used as the baseline RHC, provided the criteria for historical RHCs described in the RHC guidelines (Appendix 16) are met.

Table 2: Visit and assessment schedule during the open-label extension period

PERIOD	Name	OPEN-LABEL (OL) TREATMENT EXTENSION PERIOD										Unscheduled[2]	SAFETY FOLLOW-UP
PHASE	Name	OL Double-Dummy Uptitration Phase				OL Maintenance Phase							
		10 mg	37.5 mg			75 mg							
VISITS	Number/ Name	EOBDT 6 /OL 1	OL 2	OL 3☎	OL 4	OL 5	OL 6 ☎	OL 7	OL 8	OL 9-x		Anytime in case of clinical worsening	
	Timing	OL D1[1]	OL W4 (±3 days)	OL W5 (±3 days)	OL W 6 (±3 days)	OL W 8 (±3 days)	OL W 9 (±3 days)	OL W10 (±3 days)	OL W 12 (±3 days)	OL W 24, 48, 72, 96, … (q 24 weeks) (±5 days)	EOLT[3] (±5 days)		30 (+ 5) days after last OL dose
Screening/Administrative													
Eligibility		X											
OL study interv. dispensing		X	X			X			X	X			
Safety assessments													
Physical examination		X	X		X	X		X	X	X	X	X	X
Vital signs (BP, PR)[7]		X	X		X	X		X	X	X	X	X	X
Body weight		X	X		X	X		X	X	X	X	X	X
12-lead ECG		X				X				Weeks 24, 48			
Clinical Laboratory tests													
Central laboratory test		X	X		X	X		X	X	X	X	X	X
Serum pregnancy test[4]		X	X			X			X	X	X		X
Liver function tests[5]		X	X		X	X		X	X	monthly until 52 weeks exposure; every 12-weeks after 52 weeks exposure	X	(X)	X
Urine pregnancy test[6]										Monthly in between visits			
Efficacy assessments													
6MWT / Borg CR10 Scale®		X	X			X			X	X	X	X	
WHO FC		X	X		X	X		X	X	X	X	X	X
Clinical worsening		X	X		X	X		X	X	X	X	X	X
Ongoing participant review													
Concomitant therapy		X	X	X	X	X	X	X	X	X	X	X	X
SAEs/AEs		X	X	X	X	X	X	X	X	X	X	X	X
Optional sub-study													
Male reproductive system safety sub-study		Please refer to the schedule of assessments in Appendix 17, Section 4.											

Footnotes:

[1]The OL Day 1 visit (and associated assessments) will be combined with the EODBT visit for participants who remained on study intervention, or with PTOP 6 for participants who prematurely discontinued study intervention before Week 28 and completed the PTOP, had a CEC-confirmed CW event 28 and didn't meet any study-specific criterion for permanent discontinuation of study treatment.

[2] During the open-label extension period, an unscheduled visit must be performed in case of a suspected clinical worsening or initiation/dose escalation of PH-specific therapy. The assessments performed at the unscheduled visit include, but are not limited to: concomitant therapy, physical examination, vital signs (BP/PR) weight, post-dose 6MWT/Borg CR10 Scale® and WHO FC.

[3] EOLT will take place 2 years after the last participant has completed the fixed duration part of the DB period. In case of premature discontinuation of open-label study intervention, the EOLT visit must be performed within 7 days of taking the decision to stop study intervention.

[4] For women of childbearing potential. Additional serum pregnancy test to be performed in case of a positive urine pregnancy test.

[5] AST/ALT monitoring required monthly until Week 52 if interval between 2 regular site visits exceeds 4 weeks. After 52 weeks exposure in the OL period AST/ALT monitoring required every 12 weeks if interval between 2 regular site visits exceeds 12 weeks unless continued monthly monitoring is mandated based on local regulatory requirements . Local laboratory can be used. *Requirement for Japan:* Monthly AST/ALT monitoring is required. Whenever participants have monthly liver function tests, the following assessments should be conducted and reported in source notes: physical examination, body weight, blood pressure/pulse rate, and hematology (hemoglobin, hematocrit, and RBC count). These assessments must be recorded in the eCRF only if they are related to AEs.

[6] Women of childbearing potential only. To be performed monthly (at site or at home if the interval between 2 regular site visit exceeds 4 weeks).

[7] Phone calls to obtain information about vital status and hospitalization will be done approximately every 6 months until completion of the study for all participants who prematurely discontinued DB or OL study intervention.

Table 3: Visit and assessment schedule for participants entering the post-treatment observation period (PTOP)

Period	POST TREATMENT OBSERVATION PERIOD (PTOP)								
Duration	Up to 28 Weeks								
Timeframe[2]	PTOP 1 (Safety FU visit)[1] 30 (+5) days after last dose	PTOP 2[4] W 12 (±5 d)	PTOP 3[4] W 16 (±5 d)	PTOP 4[4] W 20 (±5 d)	PTOP 5[4] W 24 (±5 d)	PTOP 6[4] W 28 (±5 d)	PTOP 7[4,6] W 40 (±5 d)	PTOP 8[4,6s] W 52 (±5 d)	Phone call W 28 (±5 d)[5]
Safety assessments									
Physical examination	X	X	X	X	X	X	X	X	
Vital signs (BP, PR)	X	X	X	X	X	X	X	X	
Body weight	X	X	X	X	X	X	X	X	
Clinical laboratory tests									
Central laboratory test[3]	X								
Liver function tests	X								
Efficacy assessments									
6MWT / Borg CR10 Scale®	X	X	X	X	X	X	X	X	
WHO FC	X	X	X	X	X	X	X	X	
Clinical worsening	X	X	X	X	X	X	X	X	
EQ-5D-5L©		X	X	X	X	X	X	X	
PAH-SYMPACT®		X	X	X	X	X	X	X	
PHQ-8, WPAI, SF36® v2 Acute			X			X		X	
Ongoing participant review									
Concomitant therapy	X	X	X	X	X	X	X	X	
SAEs/AEs	X	X	X	X	X	X	X	X	
Vital Status									X

Footnotes:

[1] If PTOP 1 (safety follow-up visit) to be performed 30 (+5) days after intake of last dose. If PTOP 1 falls within the time-window of any other PTOP visit, the visits can be combined.

[2] From Randomization.

[3] Including Serum pregnancy test for women of childbearing potential.

[4] PTOP visits to be performed depend on the timepoint of premature discontinuation.

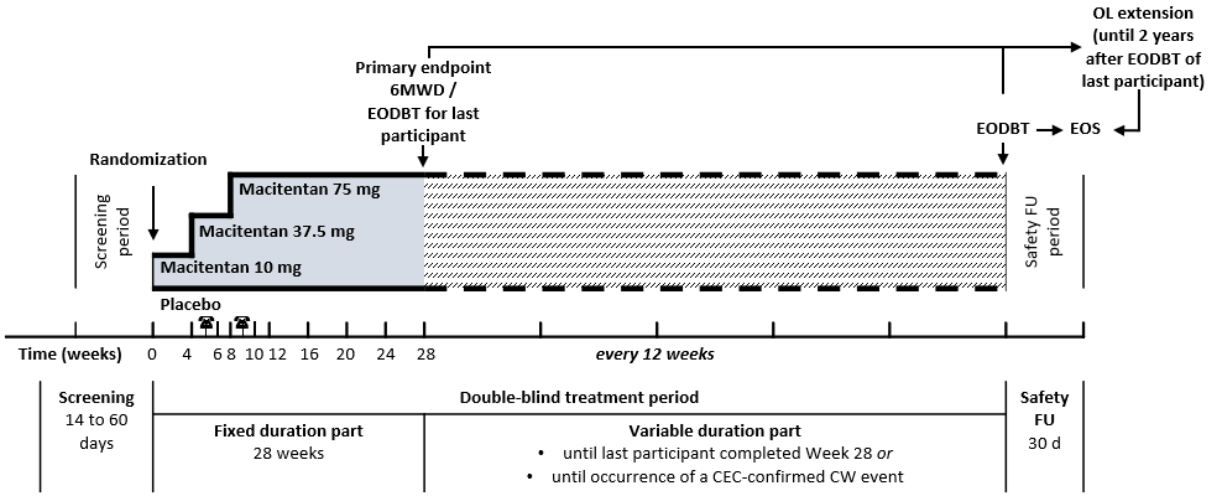
[5] Phone call obtain vital status only applies to participants who prematurely discontinued study intervention prior to Week 28 and chose not to enter or complete PTOP, provided consent was not withdrawn. Phone calls to obtain information about vital status and hospitalization will be done approximately every 6 months until completion of the study for all participants who prematurely discontinued DB or OL study intervention.

[6]PTOP 7 and 8 visits are not applicable in current protocol version 6. However, participants who consented to an earlier version of the protocol will be given the choice to maintain the previous visit schedule and enter the OL period at Week 52, PTOP 7 and 8 visits may still be performed for such participants if they prematurely discontinued study intervention.

6MWT = 6-minute walk test; AE = Adverse Event; ALT = Alanine aminotransferase; AST = Serum aspartate aminotransferase; BP = Blood pressure; CTPA = computed tomography pulmonary angiogram; D = Day; ECG = Electrocardiogram; EODBT = End of double-blind treatment; EQ-5D-5L© = Euro Quality of life-5-Dimension-5-Level; FU = Follow-up; OL = open-label; MRA = magnetic resonance angiography; NT-proBNP = N-terminal prohormone of Brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; PA = pulmonary angiography; PAH-SYMPACT® = Pulmonary Arterial Hypertension Symptoms and Impact; PFT = pulmonary function test; PHQ-8 = Patient Heath Questionnaire; PGA-S = Patient Global Assessment of Severity; PK = pharmacokinetic; PMDA = Pharmaceuticals and Medical Devices Agency; PR = Pulse rate; PTOP = Post-treatment Observation Period; RHC = right heart catheterization; SF36 = 36-item Short Form survey; SAE = Serious adverse event; V/Q = Ventilation / Perfusion; W = Week; WHO FC = World Health Organization functional class; WPAI = Work Productivity and Activity Impairment Questionnaire.

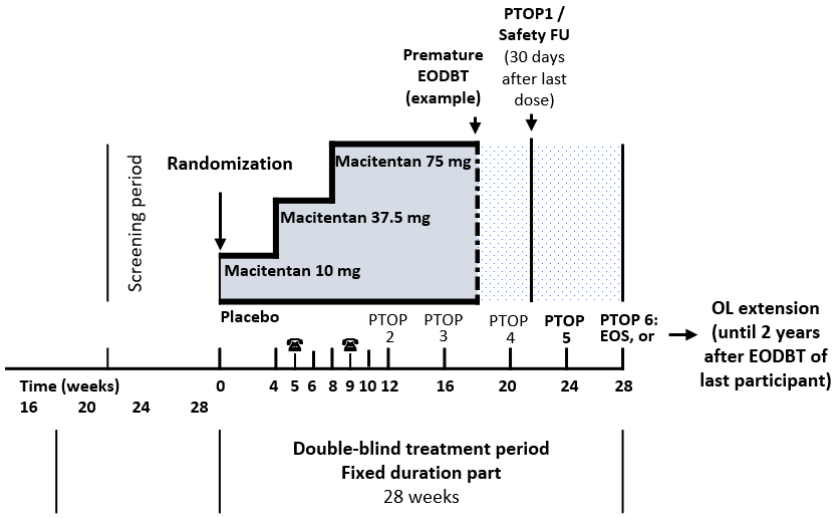
1.3 Schema

Figure 1: Schematic Overview of the Study – participants who complete the DB treatment period as per protocol



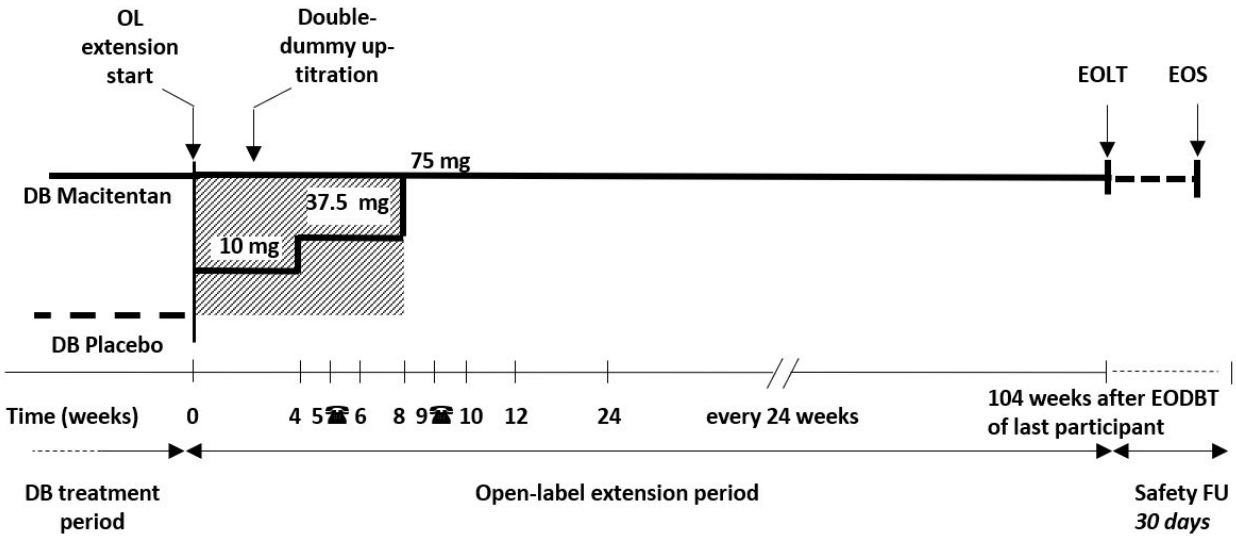
6MWD = 6-minute walk distance; EODBT = End of double-blind treatment; EOS = End of study; FU = follow-up; OL = open-label.

Figure 2: Participants who prematurely discontinue DB study intervention (example of a premature discontinuation at Week 18)



DB = double-blind; EODBT = End of double-blind treatment; EOS = End of study; FU = follow-up; PTOP = post-treatment observation period.

Figure 3: Open-label extension (eligible participants only)



DB = double-blind; EOLT = End of open label treatment; EOS = End of study; FU = follow-up; OL-open-label.

2 INTRODUCTION

Macitentan (ACT-064992, Opsumit®) is an orally active, non-peptide, potent dual endothelin receptor (ET_A and ET_B) antagonist (ERA) approved at a dose of 10 mg for the treatment of pulmonary arterial hypertension (PAH).

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the leading causes of severe pulmonary hypertension (PH), classified within World Health Organization (WHO) group 4 PH (Simonneau 2019). It is a rare, progressive pulmonary vascular disease that if left untreated, leads to progressively increasing pulmonary vascular resistance (PVR) and eventually right ventricle failure and death (Lang 2016, Jenkins 2013). The precise underlying pathogenesis of CTEPH is not completely understood, but it appears to be a consequence of a prior acute pulmonary embolism subsequent to deep vein thrombosis. The pathophysiological mechanisms that prevent the complete resolution of the embolic material in CTEPH are thought to be a misguided vascular remodeling process, which involves a combination of defective angiogenesis, impaired fibrinolysis and endothelial dysfunction (Lang 2013). CTEPH is technically a dual vascular disorder, involving not only persistent obstruction (stenoses, web and occlusions) of proximal pulmonary arteries (main, lobar and segmental) at sites of previous emboli (Simonneau 2017), but also a secondary microscopic vasculopathy affecting small resistance vessels resembling the histopathology described in idiopathic PAH (Lang 2016).

CTEPH is defined as precapillary PH (resting mean pulmonary arterial pressure [mPAP] ≥25 mmHg, mean pulmonary arterial wedge pressure [mPAWP] ≤15 mmHg) in the presence of non-resolving organized thromboemboli that are located proximally or more distally in the pulmonary arterial tree (main, lobar, segmental, subsegmental pulmonary arteries) and that persist at least 3 months after the onset of anticoagulant therapy (Gopalan 2016) At the 6th World Symposium on Pulmonary Hypertension, the mPAP threshold to define PH was lowered to 20 mmHg. The new threshold for mPAP is used in the hemodynamic confirmation of CTEPH in the present study.

Pulmonary endarterectomy (PEA) surgery is the treatment of choice for patients with symptomatic, operable CTEPH, which means CTEPH is a potentially curable form of PH. However, the extent and burden of small vessel arteriopathy constitutes the main limit to hemodynamic improvement after PEA and offers the rationale for pulmonary vasodilator therapy in some CTEPH patients with prevalent distal disease. The more pronounced the distal vascular changes, the higher the risk of surgery and the less likely the hemodynamic improvement after surgery. In addition to medical therapy, balloon pulmonary angioplasty (BPA) is an emerging therapeutic option for CTEPH patients who are technically inoperable or have been judged to have an unacceptable risk/benefit ratio for PEA. Although BPA is not yet extensively applied, it is used with increasing frequency in specialist centers worldwide and thus patients who have persistent/recurrent PH after BPA, are allowed to participate in this study (Galiè 2016).

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

The term “study intervention” throughout the protocol, refers to study drug.

The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term “participant” throughout the protocol refers to the common term “subject”.

2.1 Study Rationale

MACiTEPH is a randomized, placebo-controlled, group-sequential, adaptive trial in inoperable or persistent/recurrent CTEPH.

Macitentan 75 mg is expected to provide significant clinical benefit to CTEPH patients, including those treated with background PH-specific therapy, except ERAs and intravenous prostacyclins/prostacyclin analogs. Combination treatment with riociguat is allowed as the drug-drug interaction (DDI) data confirmed concomitant use with macitentan 75 mg is safe. MACiTEPH will include patients with persistent/recurrent CTEPH following PEA and/or post-BPA procedure, thus covering all subgroups of CTEPH populations for which medical treatment with PH-specific therapy is recommended (Kim 2019). Macitentan offers a new mode of action for the treatment of inoperable and persistent/recurrent CTEPH and addresses an important unmet medical need for an alternative treatment in this indication.

Histopathologic findings including endothelial cell dysfunction and distal pulmonary arterial remodeling are shared between PAH and CTEPH (Humbert 2010). PH-specific therapies, such as riociguat (currently the only approved therapy in inoperable and persistent/recurrent CTEPH) have shown efficacy in CTEPH, further supporting the rationale for this study

MACiTEPH will assess the effect of macitentan 75 mg on exercise capacity and is expected to confirm the role of macitentan as a first-line, as well as add-on treatment for CTEPH.

2.2 Background

For the most comprehensive non-clinical and clinical information regarding macitentan, refer to the latest version of the IB (Macitentan IB) for macitentan.

Nonclinical Studies

Pharmacology and Nonclinical Pharmacokinetics

Macitentan and its only active metabolite ACT-132577 are both potent ET_A and ET_B antagonists. ACT-132577 is approximately 5-fold less potent than macitentan in vitro. However, ACT-132577 systemic exposure in humans is about 3-fold higher than macitentan, and ACT-132577 contributes to the overall pharmacological effect of macitentan. Formation of ACT-132577 is mainly catalyzed by CYP3A4, with minor contributions of CYP2C8, CYP2C9, and CYP2C19.

Macitentan showed dose-dependent efficacy in nonclinical models of hypertension, PH, PAH, and pulmonary fibrosis. In particular, data from nonclinical in vivo experiments indicate dose-dependent increases in efficacy at higher doses, including a human equivalent dose of

approximately 100 mg daily (~30 mg/kg/day in rats) that showed improved hemodynamics and right ventricular hypertrophy (Iglarz 2008, Kunita-Takanezawa 2014). Two-week treatment with the same 30 mg/kg/day dose of macitentan in rats significantly improved pulmonary hemodynamics, pulmonary artery vascular remodeling, and right ventricle function and hypertrophy compared to vehicle-treated animals in the Sugen/hypoxia model (Kunita-Takanezawa 2014).

Toxicology

In repeated-dose toxicity studies, the heart, liver, and testes were identified as the main organs affected by treatment with macitentan. The findings were considered to be of minimal severity and reversible. Furthermore, they are considered to be either clinically manageable with appropriate patient counseling (ie, testicular findings) or not relevant to humans (ie, dog heart vascular findings) (Macitentan IB).

Exposures (based on a combination of the areas under the curve [AUCs] for macitentan and the major active metabolite) at the lowest-observed-adverse-effect levels (LOAEL) are similar to anticipated human exposures at steady state for 75 mg macitentan per day. The toxicities observed at the LOAEL were of minimal severity and reversible.

The main finding in the dog heart was coronary arterial intimal thickening, characterized by proliferation of the intimal layer. The severity of intimal thickening was generally minimal, and the incidence or severity did not increase with treatment duration. Partial to complete reversibility was noted in 16-week recovery in chronic dog studies. Similar lesions were not observed in mice or rats. The dog is a species particularly sensitive to hemodynamic changes and related coronary vascular and myocardial effects (Dogterom 1992). Coronary arterial lesions have often been described for ERAs and other marketed vasodilating drugs in dogs but not in humans (Albassam 2001, Louden 2001, Mcduffie 2006). These findings are considered a species-specific sensitivity and not relevant for humans.

Changes in the liver were largely reversible and are considered non-adverse adaptations (increased weight, hepatocellular hypertrophy) of the liver to increased metabolic demand.

Dilation of seminiferous tubules noted in rats and dogs was of low incidence and severity, often at the border of detection and was reversible in 8-16 weeks. There was no effect noted on male fertility in rats.

Macitentan was embryotoxic and teratogenic in developmental and reproductive toxicity studies, which is a known effect for this class of molecules. Macitentan was not genotoxic or phototoxic. It was not carcinogenic in mice or rats. In juvenile toxicity studies in rats, the target organs were not different from those in adult animals (Macitentan IB).

Clinical Studies

Efficacy in PAH

Efficacy was established in the SERAPHIN study, a long-term study in 742 PAH patients with predominantly WHO functional class (FC) II-III symptoms treated for an average of 2 years. Patients had idiopathic or heritable PAH (57%), PAH associated with connective tissue disorders (31%), and PAH associated with congenital heart disease with repaired shunts (8%), and were treated with macitentan monotherapy or in combination with phosphodiesterase type-5 (PDE-5) inhibitors or inhaled prostanoids (Pulido 2013).

The trial demonstrated that macitentan 10 mg reduces the risk of morbidity/mortality in patients with symptomatic PAH, with a hazard ratio (HR) vs placebo of 0.55, 97.5% confidence limits (CLs): 0.39, 0.76, p <0.0001. This represents a risk reduction of 45%. The effect of macitentan was observed regardless of whether the patient was receiving another therapy, including a PDE-5 inhibitor, for PAH (Pulido 2013).

The placebo-corrected mean change in 6MWD from baseline to Month 6 (24-26 weeks) showed an increase of 22.0 m (97.5% CLs: 3.2, 40.8, p = 0.008) with macitentan 10 mg. The WHO FC improved from baseline to Month 6 in 13% of the patients in the placebo group, compared to 22% of those in the group that received 10 mg of macitentan (p = 0.006) (Pulido 2013).

A hemodynamic sub-study in 187 subjects showed a placebo-corrected mean reduction of PVR from baseline (mean PVR at baseline for the overall SERAPHIN population was 1026 dyn·sec·cm^{-5}) to Month 6 of 38.5% (97.5% CLs: 25.7%, 49.0%) with macitentan 10 mg (Pulido 2013).

Efficacy in CTEPH

The efficacy and safety of macitentan 10 mg was evaluated in a Phase 2 study of macitentan in inoperable CTEPH (AC-055E201/MERIT-1). Results of the MERIT-1 pre-specified primary and main secondary endpoint analyses showed clinically and statistically significant beneficial effects of macitentan 10 mg od versus placebo on hemodynamics at Week 16 (PVR: geometric mean ratio = 0.84, p = 0.041) and on 6MWD at Week 24 (34 m versus placebo, p = 0.0326). The treatment effects on PVR and on 6MWD at the 10 mg od dose were consistent regardless of whether patients were receiving treatment with PH-specific therapies at baseline (Ghofrani 2017).

Human Pharmacokinetics

Based on clinical pharmacology studies conducted in healthy subjects the plasma concentration-time profile of macitentan can be described by a slow absorption with peak plasma concentrations occurring about 8 h after dosing. The apparent half-life (t½) was approximately 16 h. The active metabolite ACT-132577 was slowly formed and had an apparent t½ of about 48 hours. At steady state, ACT-132577 was present at 74% of total drug exposure. The accumulation indices for macitentan and ACT-132577 were approximately 1.5 and 8.5, respectively. After multiple-dose administration, the pharmacokinetics (PK) of both macitentan and ACT-132577 were dose

proportional over the tested dose range of 1 to 30 mg macitentan. Dose-proportional PK is also expected with the 75 mg dose based on the data collected in glioblastoma patients.

Urine represented a more important elimination route for macitentan and its metabolite than feces. Macitentan and ACT-132577 were highly bound (>99%) to plasma proteins.

No dose adjustments are required to correct for ethnicity or sex.

Concomitant use of macitentan with strong inhibitors or inducers of CYP3A4 or moderate dual CYP3A4/CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors should be avoided.

Macitentan 75 mg should be administered with food.

Drug-Drug Interactions

A single-center, open-label, single sequence, 2-part, Phase 1 study (67896062PAH1003) to investigate the effect of 75 mg macitentan once daily at steady state on the PK of riociguat, sildenafil, rosuvastatin and tadalafil in healthy subjects was initiated to support the registration of macitentan 75 mg. Part A of the study was completed and showed that co-administration of macitentan 75 mg in healthy subjects with riociguat decreased riociguat AUC by approximately 25% and C_{max} by approximately 20%. Similar reductions in riociguat exposure are observed with bosentan (27% in AUC) and omeprazole (26% in AUC). Consistent with riociguat label, these small effects are considered of limited clinical relevance and will not require riociguat dose adjustment beyond the individual dose-adjustment scheme.

In addition, the co-administration of macitentan 75 mg in healthy subjects with sildenafil did not result in a significant change in sildenafil AUC and C_{max}. Part B of the study assessing effect on rosuvastatin is currently ongoing.

Safety

The safety of macitentan 10 mg has been evaluated in a long-term placebo-controlled trial of 742 patients with symptomatic PAH, the SERAPHIN study. The mean treatment duration was 103.9 weeks in the macitentan 10 mg group and 85.3 weeks in the placebo group. The most commonly reported adverse drug reactions were nasopharyngitis (14.0%), headache (13.6%), and anemia (13.2%). The majority of adverse reactions were mild to moderate in intensity. The incidence of aminotransferases (ALT/AST) >3 × ULN was 3.4% on macitentan 10 mg and 4.5% on placebo. 2.1% of patients on macitentan 10 mg and 0.4% of patients on placebo had aminotransferase elevations >8 × ULN. The overall incidence of treatment discontinuations because of adverse events was similar across macitentan 10 mg and placebo treatment groups (approximately 11%) (Pulido 2013).

The MERIT-1 safety findings were consistent with the known safety profile of macitentan (Ghofrani 2017).

In the two Phase 1 glioblastoma studies (AC-055-115 and AC-055-118), a total of 44 patients were treated with escalating macitentan doses of up to 300 mg in combination with temozolomide. In study AC-055-115, the median dose was 150 mg daily (range 30-300 mg daily, 29 patients received doses >100 mg), and the median duration of treatment was 61 days. In study AC-055-118, a total of 6 subjects were treated with macitentan doses of either 90 mg or 150 mg for a median duration of 123 days. No unexpected adverse events (AEs) were observed in either study and in both studies, the majority of AEs were associated with glioblastoma disease progression, including those that were serious or resulted in discontinuation of treatment. No dose-limiting toxicities occurred, and no maximum tolerated dose was identified (D-16.563, D-17.238).

Since initial approval (18 October 2013), an estimated 62,819 patients had been exposed to commercial macitentan worldwide by the end of September 2019. The nature and severity of the reported events from all sources were consistent with the known safety profile of macitentan and the high morbidity and/or mortality of the underlying PAH disease and did not indicate any changes to the safety profile (Macitentan IB).

2.3 Benefit-Risk Assessment

2.3.1 Known Benefits

The clinical benefits of macitentan 75 mg od for the treatment of patients with CTEPH have yet to be established.

2.3.2 Potential Benefits

The results from the MERIT-1 study (macitentan 10 mg in inoperable CTEPH) were encouraging in terms of efficacy and safety. If the hypothesis that increased ET_B inhibition with a dose of 75 mg od further improves clinical outcomes is confirmed, macitentan 75 mg may improve exercise capacity and possibly delay time to clinical worsening in CTEPH patients (see Section 4.3).

2.3.3 Known Risks

Reproductive toxicity studies showed that macitentan is teratogenic, which is also known to be an ERA class effect. For this reason, the study will only enroll non-pregnant women (see Section 5.1) and contraception requirements are in place for women of childbearing potential. These elements are included in the protocol (see Appendix 5) and will be indicated in the Informed Consent Form (ICF).

AEs of special interest identified for macitentan 10 mg include edema/fluid retention, hypotension, liver events, anemia/hemoglobin decrease including anemia requiring blood transfusions without confounding factors (see Section 8.4.5).

2.3.4 Potential Risks

The safety and tolerability of macitentan 75 mg od for the treatment of patients with CTEPH have yet to be confirmed since doses higher than 10 mg have not been tested in patients with CTEPH. However, as indicated in Section 4.3, human safety data in healthy subjects (up to 30 mg daily) and glioblastoma patients (up to 300 mg daily in combination with temozolomide) did not identify any safety signal that would preclude studying daily doses of macitentan higher than 10 mg in patients with CTEPH.

To ensure the safety of the participants, several measures are in place:

- Conservative uptitration scheme: Participants randomized to the 75 mg macitentan arm will receive macitentan 10 mg for 4 weeks, followed by macitentan 37.5 mg for 4 weeks prior to reaching the target dose of 75 mg.
- Safety will be closely monitored throughout the study:

  Safety evaluations (see Section 8.3) will be performed at each scheduled visit during the study, as indicated in Table 1 to Table 3.

  – During the uptitration phase, bi-weekly safety visits and additional phone calls ensure early detection of signs or symptoms of potential adverse events.

  – Bi-weekly liver functions tests between Weeks 4 and 12, monthly until Week 52 and 3-monthly thereafter.

  – The investigator or the designee will document AEs as indicated in Section 8.4.

  – Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable condition is reached.
- Specific criteria for interruption or permanent discontinuation of study intervention are specified in Section 7.1
- An Independent Data Monitoring Committee (IDMC) will monitor the safety of the participants by reviewing unblinded data.
- Hepatic Adverse Events of Special Interest (HAESIs) will be reviewed by an International Liver Safety Data Review Board (ILSDRB).

During the optional hemodynamic sub-study (see Section 8.2.8), participants will undergo a right heart catherization (RHC), which may be associated with side effects (bruising or hematoma, swelling and infection, irritating sensation, heart rhythm abnormalities, low blood pressure, bleeding, general infection, collapsed lung, or clotting of the blood, mortality). The RHC will only be performed at sites able to comply with the protocol-specific RHC guidelines (Appendix 16).

2.3.5 Benefit-Risk Assessment for Study Participation

The overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- There is a clear unmet need for additional medical therapy in CTEPH.

- Only patients who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Appropriate safety measures are put in place to ensure the safety of the participants (see Section 2.3.4)

It is the investigator's responsibility to monitor the individual benefit/risk of study intervention administration, as well as the degree of distress caused by study procedures at an individual participant level, and to discontinue study intervention or the study if he/she considers that continuation would be detrimental to the participant's well-being.

More detailed information about the known and expected benefits and risks of macitentan may be found in the IB (Macitentan IB) and local Prescribing Information.

3 OBJECTIVES AND ENDPOINTS

Double-blind treatment period	
Objectives	**Endpoints**
Primary	
To evaluate the effect of macitentan 75 mg versus placebo on exercise capacity at Week 28 in participants with chronic thromboembolic pulmonary hypertension (CTEPH).	Change from baseline to Week 28 in exercise capacity (6-minute walk distance [6MWD], as measured by the 6-minute walk test [6MWT]).
Secondary	
To evaluate the effect of macitentan 75 mg versus placebo on clinical worsening up to end-of double-blind-treatment (EODBT).	Time to first Clinical Event Committee (CEC) confirmed clinical worsening up to EODBT*. Clinical worsening is defined as the occurrence of at least one of the following events: – All-cause death** – Heart and/or lung transplantation – Unplanned pulmonary hypertension (PH)-related hospitalization – PH-related deterioration from baseline identified by at least one of the following: – Persistent[a] increase in World Health Organization functional class (WHO FC) that cannot be explained by another cause (eg, viral infection) – Persistent[a] deterioration by at least 15% in exercise capacity, as measured by the 6MWD; – New or worsening signs or symptoms of right heart failure – Rescue pulmonary endarterectomy (PEA) and/or balloon pulmonary angioplasty (BPA) procedure due to worsening of PH. * Including events occurring up to 7 days after last dose of DB study intervention. **Including deaths occurring within 30 days of last dose of study intervention caused by an AE that occurs within 7 days of intake of last dose of DB study intervention.
To evaluate the effect of macitentan 75 mg versus placebo on WHO FC at Week 28.	Improvement in WHO FC from baseline to Week 28 (yes/no).
To evaluate the effect of macitentan 75 mg versus placebo on quality of life at Week 28	Change from baseline to Week 28 in • Pulmonary Arterial Hypertension – Symptoms and Impact (PAH-SYMPACT®) – Cardiopulmonary symptom domain score – Cardiovascular symptom domain score

[a] Confirmed by a second measurement performed on a different day within 2 weeks

Double-blind treatment period	
	• Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L©) utility score.
To evaluate the effect of macitentan 75 mg on daily physical activity	Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity.
Exploratory	
To evaluate the effect of macitentan 75 mg versus placebo on exercise capacity in participants with CTEPH.	Change from baseline to all assessed timepoints in exercise capacity (6MWD, as measured by the 6MWT).
To evaluate the effect of macitentan 75 mg on PH-related deaths and hospitalizations	Time to first occurrence of CEC-confirmed PH-related death* or unplanned PH-related hospitalization up to 7 days after the last dose of DB study intervention *including deaths occurring within 30 days of last dose of study intervention caused by an AE that occurs within 7 days of intake of last dose of DB study intervention.
To evaluate the effect of macitentan 75 mg versus placebo on hospitalization up to EODBT	Number of recurrent hospitalizations (all cause and related to PH worsening) up to EODBT.
To evaluate the effect of macitentan 75 mg versus placebo on low risk criteria and non-invasive risk group defined from WHO FC, 6MWD and NT-proBNP thresholds	• The proportion of participants with a total number of low-risk criteria (0, 1, 2 or 3) present at baseline and at all follow-up assessments up to EODBT • The number and % of participants within each of the noninvasive risk group (low-, intermediate- or high-risk) at baseline and at all assessment timepoints up to EODBT • The number and % of participants who's non-invasive risk improved, remained stable or worsened from baseline.
To evaluate the effect of macitentan 75 mg versus placebo on dyspnea and exertion	Change from baseline to all assessed timepoints in • Dyspnea • Exertion assessed by the Borg CR10 Scale®
To evaluate the effect of macitentan 75 mg versus placebo on NT-proBNP.	Percent of baseline NT-proBNP over time.
To evaluate the effect of macitentan 75 mg versus placebo on quality of life	Change from baseline to all assessed timepoints in: 1. PAH-SYMPACT® • Cardiopulmonary symptom domain score • Cardiovascular symptom domain score • Physical Impact Score • Cognitive/Emotional Impact Score 2. Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L©) utility 3. Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L©) VAS score 4. SF-36©

Double-blind treatment period	
	5. PGA-S
To evaluate the effect of macitentan 75 mg versus placebo on participants' depression symptoms	Change from baseline to all assessed timepoints in Patient Heath Questionnaire (PHQ-8)
To evaluate the effect of macitentan 75 mg versus placebo on participants' work and productivity	Change from baseline to all assessed timepoints in work productivity and activity impairment, assessed by the Work Productivity and Activity Impairment Questionnaire©: General Health (WPAI©: GH)
To evaluate the effect of macitentan 75 mg on daily physical activity	Change from baseline to all assessed timepoints in accelerometry parameters
To evaluate the pharmacokinetics (PK) of macitentan and its metabolite ACT-132577 in participants with CTEPH	Macitentan and ACT-132577 concentrations at all assessed timepoints
To evaluate the effect of macitentan 75 mg on ET-1 concentrations	Change from baseline to all assessed timepoints in ET-1 concentrations
To evaluate the effect of macitentan 75 mg on medical resource utilization compared to placebo	Medical resource utilization used from baseline to all assessed timepoints, as defined hereafter: – Number per year of all-cause and PH-related hospitalizations – Number per year of in-patient hospital days for all causes and PH-related causes – Number per year of emergency room (ER) visits for all causes and PH-related causes that do not result in hospital admittance
To evaluate effect of macitentan 75 mg on hemodynamic measures compared to placebo (subset of participants)	<u>Hemodynamic Sub-study:</u> • Ratio of Week 28 PVR over baseline PVR as assessed through RHC • Changes from baseline to Week 28 in the following hemodynamic variables: mean right atrial pressure (mRAP), mPAP, cardiac index (CI), cardiac output (CO), total pulmonary resistance (TPR) and mixed venous oxygen saturation (SvO2) at rest.
Safety	
To evaluate the safety and tolerability of macitentan 75 mg in participants with CTEPH.	• All-cause death up to 30 days after study intervention discontinuation • Treatment-emergent adverse events (AEs) up to 30 days after study intervention discontinuation • AEs leading to premature discontinuation of study intervention • Treatment-emergent AEs of special interest (AESI) up to 30 days after study intervention discontinuation

Double-blind treatment period	
	• Treatment-emergent serious adverse events (SAEs) up to 30 days after study intervention discontinuation • Treatment-emergent ECG abnormalities up to 30 days after study intervention discontinuation • Treatment-emergent marked laboratory abnormalities up to 30 days after study intervention discontinuation • Change in laboratory variables from baseline to all assessed timepoints during the study • Change in vital signs (diastolic blood pressure [DBP], systolic blood pressure [SBP], and pulse rate [PR]) and body weight from baseline to all assessed timepoints during the study

Open-label treatment extension period	
Objectives	**Endpoints**
Safety	
To evaluate the long-term safety and tolerability of macitentan 75 mg in participants with CTEPH.	• All-cause death up to 30 days after study intervention discontinuation • Treatment-emergent AEs up to 30 days after study intervention discontinuation • Treatment-emergent AESI up to 30 days after study intervention discontinuation • AEs leading to premature discontinuation of study intervention • Treatment-emergent SAEs up to 30 days after study intervention discontinuation • Treatment-emergent marked laboratory abnormalities up to 30 days after study intervention discontinuation • Change in laboratory variables from baseline to all assessed timepoints • Change in vital signs (DBP, SBP, and PR) and body weight from baseline to all assessed timepoints
Exploratory efficacy	
To evaluate the long-term effect of macitentan 75 mg on exercise capacity in participants with CTEPH.	Changes from baseline to all assessed timepoints in exercise capacity (6MWD, as measured by the 6MWT).
To evaluate the effect of macitentan 75 mg on time to clinical worsening up to end-of open-label treatment (EOLT).	CEC-confirmed clinical worsening up to EOLT*. Clinical worsening is defined as the occurrence of at least one of the following events: – All-cause death

Open-label treatment extension period	

	– Heart and/or lung transplantation
	– Unplanned PH-related hospitalization
	– PH-related deterioration from baseline identified by at least one of the following:
	  – Persistent[a] increase in WHO FC that cannot be explained by another cause (eg, viral infection);
	  – Persistent[a] deterioration by at least 15% in exercise capacity, as measured by the 6MWD;
	  – New or worsening signs or symptoms of right heart failure
	• Rescue PEA and/or BPA procedure due to worsening of PH.
	
	* Including events occurring up to 7 days after last dose of study intervention.

To evaluate the effect of macitentan 75 mg on WHO FC up to EOLT	Improvement in WHO FC from baseline to all assessed timepoints
To evaluate the effect of macitentan 75 mg on hospitalization up to EOLT.	Number of recurrent hospitalizations related to PH worsening up to EOLT
To evaluate the effect of macitentan 75 mg on dyspnea up to EOLT.	Change from baseline to all assessed timepoints • Dyspnea • Exertion assessed by the Borg CR10 Scale®
To evaluate the effect of macitentan 75 mg on medical resource utilization	Medical resource utilization used from baseline to all assessed timepoints, as defined hereafter: – Number per year of all-cause and PH-related hospitalizations – Number per year of in-patient hospital days for all causes and PH-related causes – Number per year of ER visits for all causes and PH-related causes that do not result in hospital admittance

[a] Confirmed by a second measurement performed on a different day within 2 weeks

Open-label treatment extension period	
• To evaluate the long term effect of macitentan 75 mg on low-risk non-invasive criteria based on WHO FC, 6MWD and NT-proBNP	• The proportion of participants with a total number of low-risk criteria (0, 1, 2 or 3) present at baseline and at all follow-up assessments up to EODBT • The number and % of participants within each of the noninvasive risk group (low-, intermediate- or high-risk) at baseline and at all assessment timepoints up to EODBT • The number and % of participants who's non-invasive risk improved, remained stable or worsened from baseline.
• To evaluate the effect of macitentan 75 mg on PH-related deaths and hospitalizations	Time to first occurrence of CEC-confirmed PH-related deaths* or unplanned PH-related hospitalization** up to 7 days after the last dose of study intervention. *including deaths occurring within 30 days of last dose of study intervention caused by an AE that occurs within 7 days of intake of last dose of study intervention ** including hospitalizations for procedure due to clinical worsening (PEA/BPA) and lung transplantation.
• To evaluate the effect of macitentan 75 mg on overall survival and hospitalizations	Time to first occurrence of • All-cause death • All-cause hospitalization.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

PRIMARY HYPOTHESIS

The null and alternative hypotheses are formulated in terms of the difference between intervention groups at Week 28, as estimated from a Mixed Model Repeated Measures (MMRM) approach utilizing all post-baseline values (Weeks 4, 8, 12, 16, 20, 24 and 28) of 6MWD changes from baseline. Refer to Section 9.1 for further details.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind (DB), placebo-controlled, multicenter, two-stage, group sequential, adaptive study of macitentan 75 mg in men and women between 18 and 80 years of age, with a diagnosis of inoperable or persistent/recurrent CTEPH.

The study includes 2 optional sub-studies:

- al hemodynamic sub-study which will be conducted at centers who are able to comply with study-specific RHC guidelines (Appendix 16).

- a male reproductive system safety sub-study which will be conducted in centers who have access to adequate facilities. The aim of the sub-study is to provide additional safety data

of chronic treatment with macitentan on testicular function in patients with PAH or CTEPH, and it will thus be offered to male participants participating in MACiTEPH or UNISUS (AC-055-315; macitentan 75 mg in PAH) (see Appendix 17). The data from this sub-study will be pooled with the data from UNISUS and analyzed independently (ie, it will not be included in the MACiTEPH CSR).

At least 144 participants will be randomized in a 1:1 ratio to macitentan 75 mg or placebo.

Treatment allocation will be stratified by

- Inoperable (with or without BPA) vs persistent/recurrent after PEA surgery (with or without BPA)
- Use of PH-specific therapies (riociguat, other PH-specific therapy, none) at baseline.

The duration of the double-blind treatment period is variable. It will last until:

- all participants either completed or prematurely discontinued the 28-Week fixed duration part. After completion of the DB period of the study, all eligible participants have the possibility of entering the OL extension.

- a CEC-confirmed clinical worsening event occurs and, in the opinion of the investigator, switching to OL macitentan 75 mg is in the best interest of the participant.

Key efficacy assessments include 6MWD and clinical worsening, as well as WHO FC, the PAH SYMPACT® and EQ-5D-5L© questionnaires and accelerometry (refer to Section 8.2). Key safety assessments will include the monitoring of adverse events, physical examinations, measurement of body weight, vital signs measurements, pulmonary function tests, electrocardiograms and clinical laboratory tests.

The study uses an adaptive design with one interim analysis. At the interim analysis, the following decisions may be taken:

- Stop the study early for futility
- Keep the sample size unchanged at 144 participants
- Increase the sample size for the second stage of the study up to a maximum of 230 participants.

The proposed sample size reassessment procedures can help mitigate the risk of misspecification of the treatment effect assumptions in any of the subgroups.

The interim analysis will be conducted by an Independent Statistical Support Group (ISSG) and the results will be reviewed by an IDMC. The interim analysis aims at futility assessment and sample size reassessment. Based on the interim analysis, sample size can increase up to a maximum of 230 participants. Details of the interim analysis are given in Section 9.4.5.

Study periods:

The study comprises the following periods:

- A screening period of at least 14- and up to 60 days
- A DB treatment period, which starts on Day 1 (Randomization, baseline) and ends on the day of last DB study intervention intake. The DB period consists of an 8-week uptitration phase and a maintenance phase. During the uptitration phase, participants will receive macitentan at a dose of 10 mg for 4 weeks followed by a dose of 37.5 mg for 4 weeks before receiving the target dose of 75 mg. The maintenance phase is divided into a 28-week fixed duration part, at the end of which the primary endpoint is assessed, and a variable duration part. Participants assigned to the placebo arm will receive matching placebo tablets during the uptitration and maintenance phase (Figure 1).
- A post-treatment observation period (PTOP) up to Week 28 for participants who prematurely discontinued DB study intervention and didn't withdraw consent. In case of premature discontinuation, the DB treatment period ends on the day of intake of the last dose and the EODBT visit is performed within 7 days of intake of the last dose of study intervention. These participants will enter the PTOP and continue to perform the visits and assessments as scheduled until Week 28 (see schedule of activities in Section 1.2). The PTOP visits to be performed depend on the timepoint of discontinuation. The PTOP1 visit corresponds to the post-treatment safety follow-up visit and may be combined with any of the subsequent PTOP visits if it falls within the same time window (Figure 2). Participants who completed PTOP up to Week 28 are eligible to enter the open-label (OL) extension period if the eligibility criteria listed in Section 5.3 are met. Participants who prematurely discontinued study intervention and chose not to enter or complete PTOP will be contacted by phone at Week 28 and their vital status will be recorded in the case report form (CRF), provided their consent was not withdrawn.
- An open-label (OL) extension period, which starts on the day of the EODBT visit and ends with the 'End of open-label treatment' (EOLT) visit. The OL period will end for all participants 104 weeks after the last participant has completed the DB treatment period. Participants who have reached the target dose of 75 mg and either completed the DB period as per protocol or experienced a CEC-confirmed clinical worsening and remained in the study at minimum up to Week 28 (either on treatment or in PTOP) are eligible for transitioning into the OL extension period, unless an exclusion criterion defined in Section 5.3 is met. Participants randomized to macitentan will continue to receive macitentan 75 mg daily. Participants randomized to placebo will receive macitentan at a dose of 10 mg for 4 weeks followed by a dose of 37.5 mg for 4 weeks prior to receiving the target dose of 75 mg. To preserve the blind of the DB treatment period, a double-dummy uptitration is performed. Both participants and sites will remain blinded to the previous DB treatment allocations during the OL extension (Figure 3).
- A safety follow-up period, which starts on the day after the last dose of study intervention and ends with a post-treatment safety follow-up visit (30 [+5] days thereafter, to collect any AEs since the last study visit).

The end of the OL extension period of the study will be announced once all participants have performed their EOLT visit or left the study.

The study results will be reported in 2 steps:

- The analysis of the DB study period will be performed when 144 participants (if there is no sample size increase at interim) have completed the fixed duration part of the DB period or prematurely discontinued the study.
- The final analysis for the study, including combined DB and OL extension, will be performed after closure of the OL extension period.

Diagrams of the study design are provided in Figure 1 to Figure 3.

Duration of the study

For an individual participant, the duration of the DB period of the study is variable, depending on the timepoint of entry into the study and whether a CEC-confirmed clinical worsening event occurred. The minimum duration is 28 weeks, and the maximum duration is estimated to be approximately 3.5 years. After completion of the DB treatment period, participants may be eligible to enter the OL treatment period, which will last until 2 years after the last participant completed the fixed duration part of the DB period. The entire study is expected to last approximately 6 years.

A diagram of the study design is provided in Section 1.3.

4.2 Scientific Rationale for Study Design

Rationale for the use of placebo

A placebo-controlled study conducted in a randomized and DB fashion provides the most definitive and rigorous method of evaluating treatment efficacy of a medical intervention. A placebo-controlled study is considered ethically acceptable due to the eligibility criteria restricting enrollment to stable CTEPH participants who may benefit from pharmacotherapy. Participants who are on Riociguat, PDE-5 inhibitors or oral or SC prostanoids at baseline are allowed to remain on these medications. The initiation and escalation of any PH-specific therapies (other than ERAs, the initiation of which requires discontinuation of study intervention) is allowed at any time during the study.

Additional measures to minimize the risks of prolonged DB treatment for the participants include:

- Exclusion of participants with unstable PH or who have a change in dose or initiation of PH-specific therapy less than 90 days prior to Randomization (see Section 5.2).
- Exclusion of participants with any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (see Section 5.2).
- After Week 28 (timepoint of assessing the primary endpoint), transition to OL macitentan 75 mg is possible in case of a CEC-confirmed clinical worsening event.
- Close monitoring by an external IDMC throughout the study.

Rationale for 2-step uptitration, each for 4 weeks

Macitentan at any dose is currently not approved in CTEPH. 40 inoperable CTEPH patients received macitentan 10 mg in a Phase 2 study (MERIT-1) which showed a safety profile that is consistent with the experience in PAH in trials and real-world data. However, macitentan has not

been studied in post-BPA or post-PEA CTEPH patients at any dose, and it has not been studied in any CTEPH patients including inoperable CTEPH at doses higher than 10 mg daily. In addition, doses of macitentan higher than 10 mg daily have not been studied in any other PH population at this time.

Therefore, to establish safety of these doses in the different CTEPH subgroups, a 2-step uptitration scheme has been implemented in this study design, first at 10 mg daily for 4 weeks, and then at 37.5 mg daily for another 4 weeks, before achieving the target dose of 75 mg daily (8 weeks from the time of Randomization). This will give the target dose a period of 20 weeks to exert its effect before measuring the primary endpoint at Week 28.

Down-titration to a lower dose of macitentan is not permitted. Participants who are unable to reach the target dose of 75 mg will be required to discontinue study intervention and enter the PTOP.

Rationale for implementing a DB period of variable duration:

The main reason for implementing a DB period of variable duration is to increase the statistical power for the time to clinical worsening (TTCW) endpoint.

Time to Clinical Worsening (TTCW) is the key secondary endpoint of the MACiTEPH study. It is considered to represent a highly clinically relevant endpoint for participants with a progressive disease such as CTEPH. Because of the relatively small sample size (a larger study is not considered to be feasible), and the anticipated low incidence of clinical worsening events, the duration of follow-up on DB treatment is critical for obtaining a sufficient number of events and thus sufficient power for the TTCW endpoint.

To increase follow-up time on DB treatment, the following modifications were made to the study design:

- The fixed duration part of the study is reduced from 52 to 28 weeks. After Week 28, the duration of the DB period will be variable, depending on the timepoint of randomization and the occurrence of a clinical worsening event (see section 4.1). The aim of the 28-week fixed duration part is to secure the primary endpoint of the study (6MWD), ie, without confounding the expected treatment effect by crossing over to OL macitentan 75mg.

- The variable duration part of the DB period is expected to result in a mean DB follow-up time of 24 months, which is twice as much compared to the previous study design (52 weeks).

Furthermore, the reduction of the fixed DB duration from 52 to 28 weeks will reduce the overall duration of the DB period by 6 months. The end of the DB period of the study will be announced once all participants have completed the 28-week fixed duration period. Participants who were randomized under protocol versions 2-5 will be given the option to transition to the OL extension at the timepoint mentioned in the consent form they initially signed (ie, Week 52).

Rationale for the open-label extension period

As CTEPH is a chronic and devastating disease in which long-term maintenance of treatment is recommended by current guidelines (Kim 2019), the aim of the open-label extension is to assess the long-term safety and tolerability, as well as the maintenance of long-term efficacy of macitentan 75mg in this disease. This is particularly relevant, as to date, the safety of macitentan has not been studied at doses higher than 10 mg od in any PH population. Furthermore, this OL extension study will give eligible participants who have completed the DB period of the study as per protocol (either on treatment or in PTOP) an opportunity to continue or to start receiving macitentan 75 mg. The earliest possible timepoint of entering the OL extension is Week 28 for an individual participant.

Rationale for 6MWD

Assessment of change in exercise capacity using the 6MWD has been used as the primary endpoint in most clinical trials involving patients with PAH and CTEPH (Rubin 2002, Galie 2005, Provencher 2006, Galie 2008, Ghofrani 2013a, Ghofrani 2013b).

In addition to pulmonary vasodilation, macitentan 75 mg is anticipated to improve vascular and right ventricular (RV) remodeling by achieving maximal ET_B inhibition, thereby improving RV function and delaying progression of RV failure (Jasmin 2001, Iglarz 2008, Iglarz 2015, Kunita-Takanezawa 2014, Nadeau 2017). The expected improvement in remodeling and cardiac performance at the higher doses is expected to translate into persistent functional gains (ie, improvement in 6MWD).

In previous studies using the 6MWD as a primary endpoint, the time to assessment after start of treatment ranged from 12 to 24 weeks (Rubin 2002, Galie 2008, Ghofrani 2013b, Ghofrani 2017). In this planned study, the 6MWD will be assessed monthly up to Week 28. At the timepoint of assessing the primary endpoint, the participants will have been exposed to the target dose of 75 mg for 20 weeks, which is deemed adequate to detect a clinically significant treatment effect.

Medical Resource Utilization Data Collection

Treatment of CTEPH with macitentan 75 mg versus placebo may result in lower utilization of medical resources; therefore, comparison will be done across intervention groups.

Rationale for Optional Hemodynamic Sub-study

CTEPH is characterized by an increased resistance to blood flow in the pulmonary vasculature quantified by PVR. In addition, PVR has strong prognostic and predictive value for clinical outcome in CTEPH (Mayer 2011, Suda 2012, Kato 2014, Ramos 2016, Richter 2017). A previous study of macitentan 10 mg in inoperable CTEPH has shown a significant reduction in PVR (see Section 2.2, efficacy in CTEPH). The aim of this sub-study is to confirm the effect of macitentan 75 mg on PVR in participants with inoperable or persistent/recurrent CTEPH. PVR and other hemodynamic variables (including but not limited to: mean right atrial pressure (mRAP), mPAP, cardiac index (CI), cardiac output (CO), total pulmonary resistance (TPR) and mixed venous oxygen saturation (SvO_2) at rest) will be measured.

4.2.1 Study-Specific Ethical Design Considerations

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

The primary ethical concerns are the administration of a dose of 75 mg macitentan which exceeds the dose of macitentan previously tested in CTEPH and approved in PAH. A justification for this dose is provided in Section 4.3.

The total blood volume to be collected (see Section 8) is considered acceptable over this time period and for this study population, based on the standard of the WHO recommendations (WHO Report).

4.3 Justification for Dose

Macitentan is approved for the treatment of PAH at a dose of 10 mg od, and the same dose (10 mg) was used in a Phase 2 study of macitentan in inoperable CTEPH (AC-055E201/MERIT-1).

ET-1 is one of the most potent vasoconstrictors known and it exerts its effects via 2 receptor subtypes: ET_A and ET_B. In physiological conditions, ET_A receptors are expressed on vascular smooth muscle cells and mediate vasoconstriction. ET_B receptors are expressed on endothelial and smooth muscle cells; endothelial ET_B receptors mediate vasodilation via nitric oxide release, while smooth muscle ET_B mediates vasoconstriction. Certain pathological conditions, including PH, lead to endothelial dysfunction with impaired NO production (Girgis 2005) and upregulation of smooth muscle ET_B receptors in the media of pulmonary blood vessels (Bauer 2002). As a consequence, endothelial mediated relaxation is lost and both ET_A and ET_B receptors mediate vasoconstriction and contribute to the detrimental effects of ET-1 (Kakoki 1999, Clozel 2006, Iglarz 2014, Iglarz 2010), suggesting superior efficacy of dual ET receptor antagonists.

Data from in vitro ET_B receptor radioligand binding assays suggest that ET_B is only partially blocked at a macitentan dose of 10 mg. Exposure-response analysis of human ET-1 levels measured in healthy subjects (AC-055-102) and glioblastoma patients (AC-055-115 & AC-055-118) suggest that inhibition of ET_B receptors can be increased by increasing the dose of macitentan above 10 mg (D-16.563, D-17.238). Based on the results of this analysis, up to 60-75% ET_B inhibition could be achieved with doses of macitentan up to 75 mg compared to the 15-20% ET_B inhibition expected with the 10 mg dose.

Human safety data in healthy subjects did not show any safety signal that would preclude studying daily doses of macitentan higher than 10 mg in patients with CTEPH. Based on the glioblastoma studies, no unexpected AEs were observed, and no dose-limiting toxicities occurred with escalating macitentan doses up of to 300 mg/day (including 14 subjects exposed to doses >100 mg

for more than 12 weeks) in combination with temozolomide. A macitentan dose of 75 mg od is expected to achieve close to maximal ET_B inhibition while having a sufficient safety margin.

In summary, macitentan at a dose of 10 mg daily showed improvements in PVR and 6MWD in patients with inoperable CTEPH. Based on animal and translational data, a dose of 75 mg od is expected to further improve clinical outcomes due to the increased inhibition of the ET_B receptor.

A detailed description of the rationale for the use of macitentan 75 mg is provided in the IB (Macitentan IB) for macitentan.

4.4 End of Study Definition

End of Study Definition

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

EOS visit

The definition of the EOS visit for an individual participant depends on the status of the participant:

Participants who didn't enter the OL treatment extension phase:

- Participants who completed the DB treatment per protocol: EOS corresponds to the Safety FU visit.
- Participants who discontinued DB treatment during the fixed duration part and entered PTOP: EOS corresponds to the PTOP 6 visit
- Participants who discontinued DB treatment during the fixed duration part and didn't enter PTOP: EOS corresponds to the Safety FU visit 30 (+5) days after the last intake of DB study treatment
- Participants who discontinued DB treatment at the end of the fixed duration part, or during the variable duration part of the DB treatment period: EOS corresponds to the Safety FU visit 30 (+5) days after the last intake of DB study treatment

Participants who entered the OL extension:

- Participants who either discontinue OL treatment prematurely or complete it per protocol: EOS corresponds to the Safety FU visit 30 (+5) days after the last intake of OL study treatment
- Participants who transition to a post-trial access option (post-trial access program, other OL study): EOS corresponds to the EOLT visit

Withdrawal of consent:

- EOS will be the last visit performed

Study Completion Definition

A participant will be considered to have completed the entire double-blind period if he or she has remained in the DB period until the end of the DB period is announced and either entered the OL extension period or had a safety follow-up (EOS) visit.

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase will not be considered to have completed the study.

A participant will be considered to have completed the OL Treatment Extension Period if he or she remained in the study until the end of the OL period is announced and has completed the safety follow-up / EOS visit or entered a continued access program.

5 STUDY POPULATION

Screening for eligible participants will be performed within 60 days before administration of the DB study intervention and includes confirmation of CTEPH diagnosis by the adjudication committee. The minimum duration of the screening period is 14 days. Refer to Section 5.5, Screen Failures, for conditions under which the repeat of any screening procedures is allowed.

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

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

5.1 Inclusion Criteria

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

1. Sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
2. Male or female ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤80 years of age.
3. CTEPH (WHO Group 4) fulfilling one of the following criteria:
   a. Inoperable due to the localization of the obstruction being surgically inaccessible (ie, distal disease) as confirmed by the adjudication committee (AC), and diagnosed based on
      - At least 2 of the following assessments in the 14 month-period prior to Randomization: Ventilation / Perfusion (V/Q) scan, pulmonary angiography (PA), computed tomography pulmonary angiogram (CTPA), magnetic resonance angiography (MRA).

- RHC at least 12 weeks after full anticoagulation[a] showing the following (at Screening or in the 24-week period prior to Randomization):
    - mPAP >20 mmHg
    - Pulmonary artery wedge pressure (PAWP) ≤15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) ≤15 mmHg
    - PVR at rest ≥240 dyn·sec/cm^5

b. Persistent/recurrent CTEPH after BPA, and deemed inoperable due to the localization of the obstruction being surgically inaccessible (ie, distal disease) as confirmed by the AC, diagnosed based on:

- At least one of the following assessments performed after the latest BPA in the 14-month period prior to Randomization: V/Q scan, PA, CTPA or MRA
- RHC at least 12 weeks after BPA and full anticoagulation[a] showing the following (at Screening or in the 24-week period prior to Randomization):
    - mPAP > 20 mmHg
    - PAWP ≤15 mmHg or, if not available or unreliable, a LVEDP ≤15 mmHg
    - PVR ≥240 dyn·sec/cm^5

c. Persistent/recurrent CTEPH after PEA (including PEA followed by BPA), diagnosed based on:

- At least one of the following assessments performed after the PEA (and latest BPA following PEA, if applicable) in the 14-month period prior to Randomization: V/Q scan, PA, CTPA or MRA
- RHC performed at least 12 weeks after PEA (or latest BPA, if applicable) and full anticoagulation[a] showing the following (at Screening or in the 24-week period prior to Randomization):
    - mPAP >20 mmHg
    - PAWP ≤15 mmHg or, if not available or unreliable, a LVEDP ≤15 mmHg
    - PVR ≥240 dyn·sec/cm^5,

4. 6MWD ≥ 100 m AND ≤ 450 m, documented by an eligibility and a baseline 6MWT. The baseline 6MWD must not differ by more than 15% from the eligibility test.
5. WHO FC ≥II
6. Participants are to receive riociguat as per local standard of care, unless it is contraindicated or unavailable
7. A woman must be (as defined in Appendix 5)
    - Not of childbearing potential, or
    - Of childbearing potential and
        - have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at Screening and a negative urine pregnancy test at Randomization.
        - practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) from Screening up to at least 30 days after last dose of study intervention.

[a] Defined as treated with either vitamin K antagonists or new oral anticoagulants (eg, factor IIa inhibitors, factor Xa inhibitors), or treated with unfractionated heparin or low molecular weight heparin.

Examples of highly effective methods of contraception are located in Appendix 5.

The criteria for inclusion in the male reproductive system safety (spermatogenesis) sub-study are detailed in Appendix 17.

5.2 Exclusion Criteria

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

Exclusion criteria related to the disease

1. Criterion modified per Amendment 4

   1.1 Acute pulmonary embolism within 3 months prior to or during Screening.
2. Criterion modified per Amendment 4

   2.1 Planned BPA during the fixed duration part of the double-blind period

Exclusion criteria related to comorbidities

3. Significant obstructive and restrictive lung disease fulfilling any of the following:
   a. Forced expiratory volume in 1 second / forced vital capacity (FEV1/FVC) <0.7, associated with FEV1 <60% of predicted value after bronchodilator administration in participants with a known or suspected history of significant lung diseases.
   b. Known moderate or severe restrictive lung disease, eg, total lung capacity or FVC <60% of predicted.
   c. Clinical suspicion of diffuse interstitial fibrosis or alveolitis, unless excluded by high resolution computed tomography.
4. Acute or chronic conditions (other than dyspnea) that limit the ability to comply with study requirements, in particular with 6MWT (eg, intermittent claudication).
5. Criterion modified per Amendment 4

   5.1 Symptomatic coronary artery disease requiring an intervention (eg, Percutaneous Coronary Intervention, Coronary Artery Bypass Graft) within 3 months prior to or during Screening or anticipated during the fixed duration part of the study.
6. Decompensated cardiac failure if not under close supervision.
7. Known and documented life-threatening cardiac arrhythmias.
8. Acute myocardial infarction within 6 months prior to, or during Screening.
9. Cerebrovascular events (including transient ischemic attack) within 3 months prior to, or during Screening.
10. Known or suspicion of pulmonary veno-occlusive disease (PVOD).

Exclusion criteria related to macitentan use

11. Criterion modified per Amendment 4

    11.1 Administration of ERAs, intravenous prostacyclins / prostacyclin analogs, or investigational treatment within 90 days prior to Randomization.
12. Criterion deleted per Amendment 4

13. Criterion modified per Amendment 4

    13.1 Change in dose or initiation of PDE-5 inhibitors, oral, inhaled or SC prostacyclins / prostacyclin analogues, prostacyclin receptor agonists or riociguat
    a. within 90 days prior to Randomization, or
    b. anticipated during the fixed duration part of the DB period .

14. Hypotension, ie, systolic blood pressure (SBP) <90 mmHg or diastolic blood pressure (DBP) <50 mmHg at Screening.
15. Severe renal dysfunction with an estimated Glomerular Filtration Rate <30 mL/min/1.73 m2 using the Chronic Kidney Disease Epidemiology Collaboration formula at Screening.
16. Known moderate to severe hepatic impairment, defined as Child-Pugh Class B or C (see Appendix 6), based on records that confirm documented medical history[a]
17. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥1.5 × the upper limit of normal (ULN) at Screening
18. Hemoglobin <100 g/L (<10 g/dL) at Screening
19. Pregnant, or breast-feeding, or planning to become pregnant, while enrolled in this study or within 30 days after the last dose of study intervention.
20. Treatment with strong CYP3A4 inducers such as rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, or St. John's wort within 30 days prior to Randomization.
21. Treatment with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or a moderate dual CYP3A4/CYP2C9 inhibitor (eg, fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (eg, miconazole, piperine), within 30 days prior to Randomization.
22. Known hypersensitivity to macitentan or drugs of the same class, or any of the excipients (eg, soy lecithin, lactose).

General criteria

23. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.
24. Criterion modified per Amendment 4

    24.1 Planned or ongoing[b] exercise training program for cardiopulmonary rehabilitation during the fixed duration part of the study.
25. Known concomitant life-threatening disease with a life expectancy <12 months.
26. RHC sub-study only: Previous RHC with serious complications, such as (but not limited to) cardiac arrest, arrhythmia requiring intervention, pulmonary hemorrhage, stroke, thromboembolic event and pulmonary hypertensive crisis

[a] The assessment for hepatic impairment must be fully documented in the medical history for participants that have clinical signs and evidence (from central and local labs) of hepatic impairments at screening

[b] Stable, long-term exercise programs that have been ongoing for more than 6 months at the time of Screening may continue

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.5 - Screen Failures, describes options for ret–sting. The required source documentation to support meeting the enrollment criteria is noted in Appendix 3.

5.3 Qualifying Criteria for Transitioning to the OL Extension

1. Successful uptitration of DB study intervention to target dose of 75 mg
2. Participant completed the DB period as per protocol up to Week 28 (either on treatment or in PTOP) at minimum
3. No pre-defined criterion for permanently discontinuing study intervention met during double-blind period (Section 7.1.1).
4. No significant decrease in hemoglobin (ie, <80 g/L (<4.9 mmol/L) or decrease >50 g/L from baseline) observed during the DB period that does not return to baseline value or within normal range, or the need for transfusion in the absence of confounding factors.

5.4 Lifestyle Considerations

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

1. Refer to Section 6.5 - Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

3. Strenuous exercise may affect study specified assessments and safety laboratory results; for this reason, it is recommended to avoid strenuous exercise within 2 hours before all planned study visits and during stays at the study site.

5.5 Screen Failures

For participants who failed Screening, the following data will be recorded in the eCRF if available:

- Date/Time of ICF signature
- Demographics (age, sex, race and ethnicity)
- Reason for screen failure and associated assessments, if applicable (eg, pulmonary function test (PFT) data in case exclusion criterion 3a is met).

Individuals who do not meet the criteria for participation in this study (Screening failure) may be rescreened twice, if the reason for non-eligibility is transient (eg, abnormal laboratory test, insufficient washout period of a forbidden medication). Assessments which are mandatory at Screening (eg, if historical data are not accepted) must be repeated at the time of rescreening.

Individuals who fail screening should discuss with their primary physician to determine their standard of care.

Participant Identification, Enrollment, and Screening Logs

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

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

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administered

Macitentan and matching placebo will be provided as film-coated tablets at dose strengths of 10 mg, 37.5 mg and 75 mg in childproof bottles. The tablets are administered orally and should be swallowed whole (ie, not crushed, split or chewed). Dosing frequency will be once a day.

The first intake of study intervention will take place at the randomization visit, after successful completion of all assessments. Thereafter, the study intervention should be administered orally once daily with food (ie, during a meal) at the same time each day, preferably in the morning.

The participants must be instructed to withhold study treatment in the morning of study visit days until all study assessments (except post-dose PK sampling, as applicable) have been performed. At uptitration visits (DB visits 3 and 6, OL visits 2 and 5), a tablet from the newly dispensed bottle must be taken.

An overview of the treatments and doses of macitentan and matching placebo is provided in Table 4.

Table 4: Treatment Overview

Study intervention name:	Macitentan	Placebo
Dose formulation	Film-coated tablets and matching placebo	
Unit dose strength(s)	10 mg 37.5 mg 75 mg	Placebo
Dosage levels	**Double-blind treatment period:** **Titration (8 weeks)** Day 1 to Week 4 (day before the visit): 10 mg od or matching placebo Week 4 to Week 8 (day before the visit): 37.5 mg od or matching placebo **Maintenance:** Fixed duration part: Week 8 to Week 28 (day before the visit): 75 mg od or matching placebo Variable duration part: Week 28 to EODBT of last participant or CEC-confirmed CW event of the individual participant, whichever occurs first: : 75 mg od or matching placebo **Open label extension period** **Double-dummy uptitration (8 weeks)**: Ex-placebo arm: Day 1 to Week 4 (day before visit): 10 mg tablet + Placebo-matching 75 mg tablet Week 4 - Week 8 (day before visit): 37.5 mg tablet + Placebo matching 75 mg tablet Ex-macitentan arm: Day 1 to Week 4 (day before visit): 75 mg tablet + Placebo-matching 10 mg tablet Week 4 - Week 8 (day before visit): 75 mg tablet + Placebo-matching 37.5 mg tablet **Maintenance:** Week 8 to EOLT: 75 mg od.	
Route of administration	Oral	
Dosing instructions	**Study intervention administration:** One tablet once a day with food, preferably in the morning.	
Packaging and labeling	Study intervention will be provided in childproof bottles containing 36 tablets each. Each bottle will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the bottle.	

EOLT = end of open-label treatment; od = once daily.

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

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

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

All study intervention supplies are to be used only in accordance with this protocol and not for any other purpose. Study intervention will be packed in medication kits containing the number of bottles required to supply enough medication until the next dispensation visit, as described in

Table 5 and Table 6.Extra bottles can be requested via interactive web response system (IWRS) if needed (eg, if a visit cannot be scheduled within the visit window).

Table 5: Study intervention dispensation schedule during the double-blind treatment period

Visit	Study intervention or matching placebo
Randomization	1 bottle
Weeks 4, 8, 12, 16, 20, 24	1 bottle
Weeks 28, 40, 52, etc	3 bottles

Table 6: Study intervention dispensation schedule during the open label extension period

Visit	Macitentan 10 mg or matching placebo	Macitentan 37.5 mg or matching placebo	Macitentan 75 mg or matching placebo	Macitentan 75 mg
OL extension start	1 bottle		1 bottle	
OL Week 4		1 bottle	1 bottle	
OL Week 8				1 bottle
OL Week 12				3 bottles
OL Weeks 24, 48, 72, 96, …				5 bottles

OL = open-label.

6.2 Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants, or their legally acceptable representatives, where applicable, must be instructed to return all original containers, whether empty or containing study intervention. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers. If the participant forgets to bring the remaining study intervention to a study visit, he/she must be instructed to not take any tablets from the remaining study intervention bottle and to return it at the next visit.

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

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3 Measures to Minimize Bias: Randomization and Blinding

Procedures for Randomization and Stratification

Central randomization will be implemented in this study.

Participants will be randomly assigned 1:1 to 1 of 2 intervention groups at the beginning of the DB period, based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

The randomization will be balanced by using permutation blocks and will be stratified by PH-specific therapy (riociguat / other PH-specific therapy / none) and inoperable (with or without BPA) vs persistent/recurrent after PEA surgery (with or without BPA)

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Randomization codes will be disclosed fully only if the double-blind period of the study is completed and the clinical database is closed. To preserve the blind of each individual participant during IDMC reviews and the planned interim analysis, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized, but only for those participants included in the analysis. An ISSG will conduct the analyses and present unblinded results to the IDMC (see Section 9.5).

Under normal circumstances, the blind should not be broken until all participants have completed the double-blind part of the study and the database is closed. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contacts the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the eCRF, the Investigator Site File, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue the scheduled evaluations and are allowed to continue study intervention.

6.4 Study Intervention Compliance

Study intervention compliance is based on study intervention accountability (see Section 6.2).

Participants will receive instructions on compliance with study intervention administration at Screening. During the course of the study, the investigator or designated study site-personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the study intervention.

6.5 Concomitant Therapy

Pre-study therapies administered up to 30 days before signing the ICF and PH-specific therapies (ongoing, initiated, or stopped) taken within 90 days of Randomization must be recorded in the eCRF at Screening.

Concomitant therapies must be recorded throughout the study from signing of the ICF onwards until the EOS visit (see Section 4.4) or date of last contact (see Section 7.3).

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include the generic name, start/end dates of administration (as well as whether it was ongoing at start of intervention and/or EOS), route, dose, frequency and indication.

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

All participants are to receive riociguat as per local standard of care, unless it is contraindicated (eg, due to co-morbidities, interaction with other essential concomitant medications, tolerability issues) or unavailable (eg, treatment not approved or reimbursed). The reason for not receiving riociguat must be documented in the participant's chart.

Participants on background PH-specific therapies at baseline should remain on the same dose throughout the study unless a change is clinically mandated based on the medical assessment performed during the corresponding visit.

The following medications are not allowed to be administered concomitantly with study intervention:

- ERAs (eg, bosentan, ambrisentan)
- Intravenous prostacyclins/prostacyclin analogs, unless used as rescue therapy (see Rescue Medication section below)
- Strong CYP3A4 inducers (eg, carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifabutin, rifapentin, St. John's wort)
- Strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) or moderate dual CYP3A4/CYP2C9 inhibitors (eg, fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (eg, miconazole, piperine) (FDA 2020)
- Any other investigational drug.

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

6.5.1 Rescue Medication

The initiation or dose escalation of PH-specific therapy (as defined below) is considered rescue pharmacotherapy. If rescue pharmacotherapy needs to be initiated outside of a regular visit, the participant must return to the site for an unscheduled visit to perform a medical assessment.

- ERAs (eg, ambrisentan, bosentan): their administration must lead to immediate discontinuation of study intervention
- Riociguat, PDE-5 inhibitors, prostacyclin, prostacyclin analogs, prostacyclin receptor agonist (Their administration will not require study intervention discontinuation and participants can remain in the study).

Rescue medication will be obtained locally as per local practice.

Rescue procedures

BPA and PEA, if performed during the study due to PH worsening, are considered rescue procedures. Participants who underwent a BPA or PEA may remain on study treatment.

The type of rescue procedure as well as the date must be recorded in the eCRF.

6.6 Dose Modification

No dose modification of the study intervention is allowed during the study. See Section 7.1 for guidance on interruption / premature discontinuation of study intervention.

6.7 Continued Access to Study Intervention After the End of the Study

Participants who have had their EOS visit before the completion of the study will be contacted by telephone to determine vital status and whether the hospitalization was required (including date, duration and reason of hospitalization [(PH-related or other], if available) approximately every 6 months[a] until completion of the study (see Section 4.4) , unless the participant has died, is lost to follow-up, or has withdrawn consent. If the information on vital status and hospitalization is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the CRF.

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of macitentan becomes available during the study or program.

At the end of their participation in the study, participants who have completed the study and are benefiting from the study intervention, as determined by their investigator, will be able to receive continued access via an another open-label extension study or via post-study independent requests from their investigators.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation

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

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety or tolerability reasons (eg, AE), it is in the best interest of the participant to discontinue study intervention.

[a] Does not apply during PTOP

- The participant is unable to reach the target dose of 75 mg (for both DB and OL study intervention).
- The participant becomes pregnant. Refer to Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information.
- Initiation of treatment with an ERA (eg, macitentan 10 mg, bosentan, ambrisentan).
- Liver aminotransferase abnormalities:
  - Aminotransferase ≥8 × ULN.
  - Aminotransferase ≥3 × ULN and associated clinical symptoms of liver injury; Eg, nausea, vomiting, fever, abdominal pain, dark urine, anorexia, itching, jaundice, unusual lethargy or fatigue, or flu-like syndrome (arthralgia, myalgia, fever).
  - Aminotransferase ≥3 × ULN and associated increase in total bilirubin ≥2 × ULN.

Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study intervention discontinuation until values return to pre-treatment levels or within normal ranges.

The ILSDRB provides ongoing assessment and advice regarding hepatic events that require further evaluation during the study.

A participant who prematurely discontinues DB study treatment during the fixed duration part is not considered as withdrawn from the study and will be asked to enter the PTOP which lasts until Week 28, provided that the subject's consent for this limited participation in the study has not been withdrawn.

The participant will be asked to return for an end-of treatment visit (EODBT) within 7 days after taking the decision to stop DB study intervention and for a safety follow-up visit 30 (+5) days after the last intake of dose of DB study intervention (PTOP1). At the premature EODBT visit, the assessments described in the Table 1 for the regular EODBT visit are to be performed. If the premature EODBT- or safety follow-up visit falls within the time-window of any of the PTOP visits, the visits can be combined.

Participants who prematurely discontinue OL study intervention during the OL extension period will return for an end-of treatment visit (EOLT) within 7 days after taking the decision to stop OL study intervention and for a safety follow-up visit 30 (+5) days after the last intake of OL study intervention. At the premature EOLT visit, the assessments described in the Table 2 for the regular EOLT visit are to be performed.

The safety follow-up visit will be waived in case the participant moves to a continued access program and in that case EOLT will be the last visit in the study.
If the decision to stop study intervention is taken at a regular or unscheduled site visit, this visit may become the premature EODBT/EOLT visit.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.1.2 Temporary Discontinuation

Participants experiencing an adverse event that precludes further dosing during uptitration will be allowed to interrupt study intervention temporarily for up to 5 consecutive days per uptitration step until their AE has resolved. During the DB maintenance- and OL period, interruption for up to 14 consecutive days is allowed. Study intervention will be reinitiated at the dose it was interrupted unless the interruption was more than 5 or 14 consecutive days, respectively. If after study intervention re-introduction, the AE appears again and is not explained by another medical condition, the study intervention should be discontinued. More than one episode of study intervention interruption is allowed.. Longer interruptions (ie, > 5 consecutive days during each DB up-titration step, > 14 consecutive days during the DB maintenance- and OL period) must lead to permanent study intervention discontinuation.

Study intervention interruption is mandatory in case of:

- **Liver aminotransferase abnormalities:**
  - Liver aminotransferases (ie, ALT and/or AST) ≥3 and <8 × ULN.

    Perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase within 1 week. If AST and/or ALT elevation is confirmed, continue to monitor aminotransferases, total and direct bilirubin, and alkaline phosphatase levels weekly until values return to pre-treatment levels or within normal ranges. If the aminotransferase values return to pre-treatment levels or within normal ranges, and if the potential benefits outweigh the risks, reintroduction of study intervention can be considered. The advice of a hepatologist is recommended.

    Liver aminotransferase levels must be checked within 3 days after re-introduction, then again after a further 10 to 14 days and thereafter, if results remain within normal levels, per the normal assessment schedule described in Section 8.3.5.

    All liver aminotransferase abnormalities leading to study intervention interruption or discontinuation must be recorded as AEs (see Section 8.4.5).

- **Hemoglobin abnormalities**

  In the case of a hemoglobin decrease from baseline of >20 g/L during the study, a re-test must be performed within 10 days; additional laboratory evaluations may include, but are not limited to, any of the following:

  - Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration);
  - Peripheral blood smear;
  - Reticulocyte count;
  - Iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation);
  - Lactate dehydrogenase; and

- Indirect bilirubin.

If hemoglobin remains >20 g/L below baseline value at subsequent visits, further re-tests are to be performed as per investigator's judgment.

This work-up should not result in study intervention interruption or discontinuation, unless clinically mandated based on the investigator's judgment, or in the following situation (unless clearly unrelated to study intervention, eg, hemoglobin decrease due to a bleeding event):

- A decrease in hemoglobin to <80 g/L (<4.9 mmol/L).
- A decrease in hemoglobin from baseline of >50 g/L.
- The need for transfusion in the absence of confounding factors.

Re-introduction of study medication can be considered if hemoglobin recovery, defined as a return of hemoglobin to within 20 g/L of the baseline value or within normal range, is achieved.

- **Administration of a forbidden medication (except ERAs)**

Study treatment must be interrupted if the participant requires treatment with a forbidden medication (see Section 6.5). Study treatment can be re-introduced if the forbidden treatment is discontinued and the time window defined above is not exceeded. Initiation of an ERA will require study intervention to be discontinued permanently.

7.2 Participant Discontinuation/Withdrawal From the Study

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

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

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

When participants are withdrawn from the main study, they are also withdrawn from the hemodynamic sub-study. Participants can be withdrawn from the sub-study while continuing the main study.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms (ie, telephone call at Week 28) that the participant agreed to when signing the consent form apply as local regulations permit.

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

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

7.2.1 Withdrawal from the Use of Research Samples

A participant who withdraws from the study or who withdraws consent for optional research samples while remaining in the study will have the following options regarding the optional biomarker research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for the use of optional research samples, in which case the samples will be destroyed. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

7.3 Lost to Follow-up

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

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

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

participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Activities (SoA) summarizes the frequency and timing of efficacy, PK, biomarker and safety measurements applicable to this study. For all visits, the participants must be seen or called on the designated day with an allowed visit window per the Schedule of Activities (SoA)**.** If it is not possible to complete all assessments on the same day, a visit may extend to more than 1 day within the allowed time-window.

DB Visits 5 (Week 6) and 8 (Week 10), and OL Visits 4 (week 6) and 7 (Week 10), can be conducted either at site or by a local registered nurse, or any other appropriately trained person, followed by a site telephone call.

The following order of assessments is recommended, as applicable:

1) PAH-SYMPACT® completed at participant's home, 7 consecutive days prior to visit (when applicable).
2) EQ-5D-5L©, followed by PHQ-8, SF-36®, WPAI:GH (any order)
3) ECG
4) Vital signs, body weight, and physical examination
5) WHO FC
6) 6MWT and Borg CR10 Scale® (; pre- and post-6MWT)
7) Blood samples (PK, hematology and clinical chemistry tests, NT-proBNP, +/- biomarkers)
8) RHC (if applicable)*
9) Study intervention intake
10) Blood samples for post-dose PK (2-10 hours post-dose)

*If RHC is performed, it must be done after the 6MWT

It is recommended to complete/conduct patient-reported outcome (PRO) assessments before any tests, procedures, or other consultations to prevent influencing participant perceptions.

Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed.

Unscheduled Visits

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

An unscheduled visit must be performed in case of suspected clinical worsening or initiation/dose escalation of PH-specific therapy outside of a regular visit. At unscheduled visits performed due

suspected clinical worsening, physical examination, vital signs (blood pressure/pulse rate), weight, laboratory assessments, 6MWT/Borg CR10 Scale® and WHO FC must be done. Other assessments are done per investigator's discretion.

The date of the visit and the reason for the visit, as well as data related to study-specific assessments performed at unscheduled visits, will be recorded in the eCRF.

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

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 260 mL per year. The amount of blood collected during each visit ranges from approximately 15 mL (visits with safety labs only) to 25 mL (visits with safety labs, PK and biomarker samples). During the OL extension period, the amount of blood collected per visit will not exceed 15 mL. These estimates are without considering the amount of blood to be withdrawn for the optional male reproductive system safety sub-study (refer Appendix 17 for corresponding details).

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure
- Laboratory manual, requisition forms, and sampling supplies
- IWRS Manual
- PRO questionnaires, PRO completion guidelines, and electronic devices
- eCRF completion guidelines
- ECG device and manual, as required
- SAE Form, SAE completion guidelines, and SAE fax cover page
- Pregnancy notification form and pregnancy form completion guidelines
- Study participant card
- 6MWT starter kit
- ICF template
- Accelerometer
- Additional equipment and information, as needed.

8.1 Demographics and Baseline Characteristics

Demographic and baseline characteristic data to be collected on all randomized participants include: age, sex, race and ethnicity (where local regulations permit), date of the initial CTEPH diagnosis, 6MWD, WHO FC, date of most recent CTEPH hospitalization, number of previous

hospitalization for CTEPH within 6 months prior to Screening, Child Pugh Score for participants with known hepatic impairment, and signs and symptoms of right heart failure.

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

The following specific medical history will be captured in the CRF at Screening:

- Pulmonary embolism
- Deep vein thrombosis
- Thrombophilic risk factors (eg, Lupus anticoagulant, anticardiolipin antibody, deficiency of natural anticoagulants (protein C, protein S, antithrombin), high concentration of factor VIII
- Right heart failure
- Splenectomy
- Ventriculoatrial shunt
- Inflammatory bowel disease
- Osteomyelitits
- Indwelling catheters and leads (Pacemaker, automated implantable cardiac defibrillator, dialysis catheters, permanent intravenous lines and catheters)

8.1.1 Eligibility Adjudication Procedure

Following the Screening visit, anonymized data (listed in Table 7) of all participants judged by the investigator to have technically inoperable or persistent/recurrent CTEPH, and fulfilling all other eligibility criteria, will be submitted to the adjudication committee for confirmation of eligibility and a scientific and medical plausibility check.

Table 7: Data required for adjudication procedure

	Inoperable CTEPH	**Persistent/recurrent CTEPH after BPA**	**Persistent/recurrent CTEPH after PEA****
RHC*	X	X	X
Imaging assessments	≥ 2†	≥ 1‡	≥ 1‡
Historical surgery & intervention report	–	X	X
Medical history form	X	X	X

BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PEA = pulmonary endarterectomy; RHC = right heart catheterization.

* RHC must be performed at least 12 weeks after start of full anticoagulation and at least 12 weeks after last surgical (PEA) or interventional (BPA) treatment for participants with persistent/recurrent CTEPH. If no historical RHC results are available, a RHC must be performed during the Screening period (submission of RHC tracing is optional).
** Includes PEA followed by BPA.
† Ventilation/perfusion (V/Q) scan, pulmonary angiography (PA), computed tomography pulmonary angiogram (CTPA), magnetic resonance angiography (MRA) performed in the 14-month period prior to Randomization
‡ V/Q scan, PA, CTPA, MRA performed in the 14-month period prior to Randomization after PEA and/or BPA

The imaging assessments will be performed as per local routine practice, and the data will be transferred from the investigational site to the AC via a central image processing center.

The investigator will await the eligibility assessment from the AC before informing the participant and performing the randomization visit.

A separate manual is provided to the investigational sites for guidance on the adjudication procedure (eg, requested data, transfer of data to the central image processing center, etc.).

8.1.2 Clinical Events Adjudication Procedure

All clinical worsening events will be adjudicated in a blinded manner by a CEC. Participants who experienced a CEC-confirmed clinical worsening event during the variable duration part of the DB period will be eligible to enter the OL extension period, provided that the criteria listed in Section 5.3 are met and switching to OL macitentan 75 mg is considered to be the best treatment option for the participant.

Participants who experienced a CEC-confirmed clinical worsening event during the fixed duration part will be eligible to enter the OL phase after having completed the assessments up to Week 28 (Visit 13/PTOP 6), provided the criteria listed above are met.

Transitioning to OL study intervention in case of a CEC-confirmed clinical worsening event is not mandatory; participants may remain on DB study intervention.

The investigator is requested to prepare a narrative of the participant's condition at baseline (eg, intensity/severity of the symptoms and their impact on daily life) and how it changed during the clinical worsening event. The narrative and any other relevant supportive data (eg, routine assessments such as NT-proBNP, RHC, MRI; hospital discharge summaries, as applicable) will be made available to the CEC to facilitate the adjudication. Full details for this procedure, as well as the composition and operation of the CEC, are provided in the CEC charter.

8.2 Efficacy Assessments

8.2.1 6-minute Walk Test

The 6MWT is a standardized test that measures the distance walked in 6 minutes (ATS Statement 2002). It will be performed at the timepoints indicated in the schedule of activities (see Section 1.2).

During the Screening period, an eligibility 6MWT, followed by a baseline 6MWT must be performed. The baseline test must be performed in the 1-week period prior to Randomization or at Randomization. For the participant to be eligible for randomization into the study, the distances walked during the eligibility and the baseline test must be ≥100 and ≤450 m, and the relative difference (ie, the absolute difference divided by the mean × 100) between the two tests must be ≤15%. In case the relative difference is >15%, a third test can be performed (including Borg CR10 Scale®). If the relative difference between the third and the second 6MWT is ≤15%, the participant is eligible and the third test (including Borg CR10 Scale®) will be considered as the baseline test. If 2 6MWTs are performed on the same day, the interval between them must be at least 2 hours.

For participants who have not previously performed a 6MWT, a training test will be performed in addition (and prior) to the eligibility and the baseline 6MWT. Data from the training test are not collected.

If a 6MWT cannot be performed at a scheduled visit beyond Visit 2 or at an unscheduled visit, a reason must be provided (ie, PAH-related or other).

If the participant wears a mask during the 6MWT, this will be documented in the eCRF.

Detailed guidelines on correct execution of the 6MWT are provided in Appendix 7.

8.2.2 Borg CR10 Scale®

Dyspnea and exertion will be assessed by the Borg CR10 scale® (Borg 1982, Borg 1998). The instructions on how to use the scale (Section 10.8) must be provided to the participant at Screening, prior to performing the first 6MWT. Dyspnea and exertion will be evaluated just before and after the 6MWT.

8.2.3 Clinical Worsening

Presence of clinical worsening must be assessed as indicated in the schedule of activities (Section 1.2). Clinical worsening is defined as the occurrence of at least one of the following events:

- All-cause death**
- Heart and/or lung transplantation
- Unplanned[a] PH-related hospitalization
- PH-related deterioration identified by at least one of the following:
  - Persistent[b] increase in WHO FC that cannot be explained by another cause (eg, viral infection);
  - Persistent[b] deterioration by at least 15% in exercise capacity, as measured by 6MWD
  - New or worsening signs or symptoms of right heart failure
- Rescue PEA and/or BPA procedure due to worsening of PH

[a] Not planned at study entry

[b] Confirmed by a second measurement performed on a different day within 2 weeks

**Including deaths occurring within 30 days of last dose of study intervention caused by an AE that occurs within 7 days of intake of last dose of DB study intervention.

The participant must be assessed for progression of PH-related symptoms including clinical signs of right ventricular failure. Any assessment deemed necessary by the investigator to assess worsening of PH (eg, Imaging and/or cardiac catherization, NT-proBNP) may be performed.

For clinical worsening, the investigator must carefully assess if the deterioration of the participant's condition (eg, worsening in exercise capacity or functional class) is related to the underlying PH or can be explained by an alternative cause, such as the exacerbation of concomitant illness or lack of adherence to medication intake.

If a repeat 6MWT cannot be performed due to PH-related deterioration, this needs to be documented in the eCRF.

An unscheduled visit must be performed in case of suspected clinical worsening or initiation/dose escalation of PH-specific therapy outside of a regular visit (see Section 8).

8.2.4 Risk Categories for Clinical Worsening and Death

This study will include endpoints looking at changes in the non-invasive risk criteria (WHO FC, 6MWD, NT-pro-BNP), to assess treatment effect on the number of low-risk criteria or on changes in risk category throughout the study and the correlation between baseline risk category and prediction of clinical worsening and death.(Boucly 2017; Hoeper 2017)

Table 8: An outline of risk stratification strategy

Variable	Low risk category	Intermediate-risk category	High-risk category
WHO FC	I, II	III	IV
6MWD (m)	>440	165-440	<165
NT-proBNP (ng/L)	<300	300-1400	>1400

6MWD = 6-minute walk distance; NT-proBNP = N-terminal pro B-type natriuretic peptide; WHO FC = World Health Organization Functional Class.

Based on the thresholds defined in Table 8 for each of the variables, a participant's risk at a given assessment timepoint is graded as 1to 3 (1: low risk, 2: intermediate risk and 3: high risk) and the sum of the grades is divided by the number of available variables and rounded to the next integer to define the non-invasive risk group (Hoeper 2017).

8.2.5 WHO Functional Class

WHO FC will be assessed at all visits (see Appendix 9) When applicable, WHO FC must be performed before the 6MWT.

8.2.6 Accelerometry

The daily life physical activity of the participant is assessed using an accelerometer. The accelerometer is given to the participant at Screening and is to be worn daily on the wrist of the

non-dominant hand (ambidextrous participants may wear it on either wrist) during waking hours until Week 28. The minimum wear time duration during Screening is 14 days.

Sites are able to access the participants' wear time compliance data through a web portal. Should corrective actions be necessary, the participant may be contacted by the site staff (eg, by telephone call, text message).

The actigraphy device does not display collected data, ie, the participants do not have access to their activity measurements, as this could influence their behavior.

The vendor will derive activity counts and will provide daytime activity and time (minutes) spent in sedentary, light, moderate and vigorous physical activity based on these activity counts. These data are transferred to Actelion.

Participants must return the actigraphy device to the site at Week 28/Visit 13. The devices will be returned to the vendor. Upon request, participants will be provided with a report summarizing their individual activity levels after database closure.

8.2.7 Patient Reported Outcomes

The following PRO instruments will not be administered to illiterate participants and will not be administered to a participant when the instrument is not available in a language that can be easily understood and read by the participant. It is recommended that the PROs are completed prior to any clinical assessments. Preferably, participants should complete the PROs while waiting for their appointment before any interaction with health care providers to avoid any potential bias in their responses.

All PROs will be completed by the participant on an electronic device either at home (PAH-SYMPACT®) or at the site on the day of the visits (all other PROs). Participants will be trained in the use of the electronic devices by site staff.

Refer to the schedule of activities for the timing and frequency of completion of the PROs.

8.2.7.1 PAH SYMPACT®

The PAH-SYMPACT® (Appendix 10) is a PRO instrument that was developed by Actelion Pharmaceuticals Ltd (Chin 2018). This questionnaire has been developed and validated for use in PAH patients. It is now being tested in CTEPH patients.

The PAH-SYMPACT® consists of two parts:

- The symptom part is completed for the 7 consecutive days prior to the visit at site (ie, starting 7 days before the scheduled visit date).
- The impact part is completed once, on the seventh day of the symptom's diary data collection period, together with the symptom part (ie, in the evening).

The PAH-SYMPACT® will be administered as indicated in the schedule of activities (see Section 1.2). The participant will be instructed to complete the PAH-SYMPACT® questionnaire in the evening before bedtime.

The PAH-SYMPACT® will be administered via a hand-held mobile device that participants take home. Participants will be trained on the use of the mobile device by the site staff during Screening. Data will be transferred to an electronic database upon completion of the questionnaire. Under exceptional circumstances (eg, participant is not comfortable with using the mobile device despite adequate training, technical problems) and upon prior approval from the sponsor, the paper-based PAH-SYMPACT® questionnaire can be provided to participants. The answers provided by the participants will be entered into the Sponsor's database by site staff.

To ensure compliance, the site will receive a notification approximately 10 days prior to the corresponding scheduled visits. The site will contact the participants (eg, via phone or text messages; as agreed with the participants) to remind them to charge the device and start completion of the PAH-SYMPACT®. The site will be notified in case the questionnaire hasn't been completed as per protocol and will implement appropriate corrective actions (contacting/re-training participants). If the PAH-SYMPACT® was not completed (ie, less than 4 days of data available) prior to a visit, the participant will be instructed to complete the PAH-SYMPACT® for the 7 consecutive days following a visit (except randomization and Week 28).

The data from the mobile device will be collected by the vendor, who will send the results to Actelion.

8.2.7.2 EQ-5D-5L© Questionnaire

The EQ-5D-5L© is a standardized instrument for use as a measure of health outcomes (Janssen 2013). The EQ-5D-5L© (Appendix 11) will be administered as indicated in the schedule of activities (see Section 1.2). Each participant will enter his/her scores on an electronic device.

8.2.7.3 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI©: GH) V2.0

The WPAI©:GH (Appendix 12) is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to general health. It has a recall period of 1 week (Reilly 1993).

8.2.7.4 SF-36® v2 Acute Questionnaire

The SF-36®v2 Acute Questionnaire (SF-36®v2 Health Survey© 1992, 2000, 2010, 2012 by Medical Outcomes Trust and Quality Metric Incorporated) is a 36-item short form survey used to assess the participant's quality of life (Appendix 13).

In the SF-36®v2 Acute Questionnaire, participants are instructed to rate their health and capacity to perform activities of daily living in eight domains including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health during the last week. Raw domain scores are determined and transformed to a 0-100 scale as described in the SF-36®v2 manual. Individual domain scores are used to determine

the physical and mental component summary scores as described in the SF-36®v2 manual (Maruish 2011).

8.2.7.5 Patient Health Questionnaire-8 (PHQ-8)

The Patient Health Questionnaire-8 (PHQ-8, Appendix 14) is a questionnaire containing 8 items to measure the presence and severity of depression a participant is experiencing (Kroenke 2001).

8.2.7.6 Patient Global Assessment of Severity

The PGA-S (Appendix 15) is a 6-point single item self-evaluation scale. Participants will be asked to rate the overall severity of their disease on the day of administration, with responses of none, very mild, mild, moderate, severe or very severe.

8.2.8 Right Heart Catheterization

The diagnostic RHC must be performed at least 12 weeks after full anticoagulation. For participants who underwent PEA or BPA, the time between the procedure and the RHC must be at least 12 weeks.

The diagnostic RHC is performed at Screening according to the site's own standard procedures. If the RHC was performed in the 24-week period prior to Randomization, the RHC does not need to be repeated at Screening.

Optional RHC sub-study:

Participants who consent to participate in the hemodynamic sub-study are required to have an RHC at Screening and at Week 28, following the RHC guidelines provided in Appendix 16. No minimum or maximum number of participants is pre-specified due to the optional nature of the sub-study[a]. If an RHC was performed in the 60-day period prior to Randomization, and the criteria for historical RHCs defined in Appendix 16 are met, the RHC does not need to be repeated at Screening. PH-specific therapy must be stable for at least 90 days prior to the baseline RHC.

It is recommended to keep the dose of diuretics stable for 7 consecutive days prior to the Screening- and Week 28 RHC.

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

Calculated hemodynamic parameters:

- Pulmonary vascular resistance (dyn·sec/cm^5) $PVR = \frac{mPAP - PAWP}{CO} X 80$
- Total pulmonary vascular resistance (dyn·sec/cm^5) $TPR = \frac{mPAP}{CO} X 80$

[a] For participants enrolled in Japan, the participation in the sub-study is mandatory based on an agreement with PMDA.

- SVR (dyn·sec/cm5) = [(mSAP -mRAP)/CO] X80
- mSAP (mmHg) = (2 × dSAP + sSAP)/3
- CI (liters/min/m2) $CI = \frac{CO}{BSA}$
- Diastolic pulmonary vascular pressure gradient (mmHg) = *diastolic PAP – PAWP*
- Transpulmonary gradient (mmHg) (TPG): *mPAP-PAWP*
- CO: refer to Appendix 16
- Body surface area (m^2) = 0.007184*(weight$^{0.425}$)*(height$^{0.725}$) with weight expressed in kg and height in cm.

8.3 Safety Assessments

Safety and tolerability will be evaluated throughout this study from signing of the ICF onwards until the EOS visit (see Section 4.4) or date of last contact (see Section 7.3).

The standard safety assessments to evaluate the safety and tolerability of macitentan in this study include reporting and follow-up of (S)AEs, pregnancies, vital signs, physical examination, ECG, and safety laboratory tests.

Details regarding the IDMC and the ILSDRB are provided in Section 9.5 and Section 8.4.5, respectively.

Adverse events will be reported and followed by the investigator as specified in Section 8.4, Adverse Events and Serious Adverse Events and Appendix 4.

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

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached or until the participant has been deemed lost to follow-up (see Section 7.3).

The study will include the following evaluations of safety and tolerability according to the time points provided in the schedule of activities (see Section 1.2).

8.3.1 Physical Examination

Physical examination at Screening, EODBT and EOLT includes the examination of general appearance, heart (including signs of right ventricular failure), lungs, abdomen, skin, extremities/peripheral vascular assessment, eyes, ears, nose, throat, neck (including thyroid), lymph nodes. At interim visits, a more focused/shorter physical exam will include the examination of general appearance, heart (including signs of right ventricular failure), lungs, abdomen and extremities. If indicated, based on medical history and/or symptoms, additional exams may be performed as per investigator's discretion.

Height will be measured without shoes at Screening.

Body weight will be measured at all visits in indoor clothing and without shoes, using the same scale. It is recommended to measure body weight at approximately same time (with respect to last meal) at all visits.

Participants will be instructed to monitor their body weight at home at least once per week from Randomization up to Week 12, and to contact the study site if they notice a weight increase of ≥5 kg / 11 lbs after the start of treatment. It is recommended that the participants always weigh themselves under similar conditions, eg, every morning before breakfast. The participants will receive a weight card on which body weight measurements can be recorded manually and must be instructed to bring the card along at each visit.

An unscheduled visit may be considered in case of significant weight increase or clinically relevant signs and symptoms of edema and/or fluid retention.

8.3.2 Vital Signs

SBP and DBP and radial pulse measurements will be assessed in triplicate, in a supine or sitting position, at all visits. It is recommended that the participant is allowed to rest for at least 5 minutes prior to the first reading, and to perform the triplicate measurements at least 2 minutes apart. It is also recommended that measurements are performed on the same arm and in the same position (sitting or supine), using the same device by the same operator throughout the study for an individual participant.

8.3.3 Pulmonary Function Tests

Post-bronchodilator pulmonary function tests (PFTs; FEV_1 and FVC) will be performed at Screening for participants with a known or suspected history of significant lung disease. Historical PFT data obtained within 12 months prior to Screening are accepted, provided there is evidence in the source documentation that the participant's pulmonary status has been stable/unchanged during this time and the results are considered to be reliable by the investigator. Predicted normal values for FEV_1 and FVC will be used to determine eligibility.

8.3.4 Electrocardiograms

A single standard 12-lead ECG will be performed at timepoints indicated in the schedule of activities (see Section 1.2). ECG traces will be sent to a central reader for interpretation. Results will be communicated back to the site and sent electronically to the sponsor.

It is recommended to perform the ECGs in a quiet setting without distractions (eg, television, cell phones), to allow the participant to rest in a supine position for at least 5 minutes before ECG collection. As much as possible, participants should refrain from talking or moving their arms and legs.

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

8.3.5 Clinical Safety Laboratory Assessments

Details about the collection, sampling, storage, shipment procedures and reporting of results and abnormal findings can be found in the central laboratory manual. The actual dates of sample collection must be recorded in the eCRF and laboratory requisition form.

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 2 at timepoints indicated in the schedule of activities (see Section 1.2). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

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

For monthly (3-monthly after 52 weeks exposure in the DB or OL periods, unless continued monthly monitoring is mandated based on local regulatory requirements) AST/ALT monitoring in between visits, a local laboratory can be used. If the local laboratory results show an increase in AST/ALT ≥3× ULN, the participant must return to the site and the AST/ALT re-test must be performed centrally. Only abnormal local laboratory results must be recorded in the eCRF.

Requirement for Japan: Monthly AST/ALT monitoring is required. Whenever participants have monthly visit for liver function tests, the following assessments should be conducted and reported in source notes: physical examination, body weight, blood pressure/pulse rate, and hematology (hemoglobin, hematocrit, and RBC count). These assessments must be recorded in the eCRF only if they are related to AEs.
Exceptional circumstances that will require recording of local laboratory results of the parameters listed in Appendix 2 (with corresponding normal ranges) include hospitalization of the participant due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If two or more consecutive central laboratory samples are lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time-window and these test results are available.

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

Pregnancy tests:

For women of childbearing potential, a serum pregnancy tests will be performed at the frequency defined in the schedule of activities. At randomization and if the interval between site visits exceeds 1 month, a urine pregnancy test must be performed at home on a monthly basis. The investigator/delegate will follow-up on the results of the urine pregnancy test during the monthly telephone call and record the result of the test in the eCRF. If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately, and the study intervention must be discontinued until pregnancy is ruled out.

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

8.4 Adverse Events and Serious Adverse Events

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

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

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 4.

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

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until the EOS visit (see Section 4.4) or date of last contact (see Section 7.3). Serious adverse events, including those spontaneously reported to the investigator until the EOS visit (see Section 4.4) or date of last contact (see Section 7.3) must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events, including deaths, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, without undue delay, and under no circumstances later than 24 hours following knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form (contact details are provided on the SAE form), which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax) or sent via e-mail.

New SAEs occurring after the EOS or last contact must be reported to Global Medical Safety within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study intervention.

8.4.2 Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4.

8.4.3 Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.4.4 Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. For more information on the action that should be taken towards study intervention in case a participant becomes pregnant during the study, please refer to Section 7.1.1.

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

Pregnancies must be reported as an AE in the eCRF and any AE associated with the pregnancy occurring until the EOS visit (see Section 4.4) or date of last contact (see Section 7.3) must be reported as a separate AE in the eCRF.

Any SAE occurring during the pregnancy must be reported as an SAE as described in Section 8.4.1.

8.4.5 Adverse Events of Special Interest

Adverse events of special interest include:

- **Hypotension:** symptomatic hypotension or potentially clinically meaningful decrease in blood pressure, not explained otherwise by any potential confounding factor
- **Edema/fluid retention:** clinically relevant signs and symptoms of edema and/or fluid retention (see Section 8.3.1)
- **Hemoglobin decrease/anemia:** events of hemoglobin decrease from baseline of >20 g/L should be reported in the hemoglobin level abnormalities eCRF page for identification of confounding factors.
- **Liver events:** liver aminotransferase abnormalities (ie, ALT and/or AST) ≥3 × ULN) should be reported in the liver abnormalities eCRF page for identification of confounding factors. All events of ALT (or AST) ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event.

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

An ILSDRB, an external expert committee of hepatologists, has been appointed to monitor all sponsor's studies with macitentan, and to provide ongoing assessment and advice regarding hepatic AEs of special interest that require further evaluation during the study.

8.5 Treatment of Overdose

For this study, any dose of macitentan greater than 75 mg within a 24-hour time period will be considered an overdose. In the event of an overdose, standard supportive measures must be taken, as required, and the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted.
- Closely monitor the participant for AE/SAE and laboratory abnormalities as clinically indicated
- Obtain a plasma sample for PK analysis within 3 days from the date of the overdose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

8.6 Pharmacokinetics

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

All participants will undergo sparse PK sampling in the study; sparse sampling consists of a pre-dose and a 2-10 hours post-dose PK sample.

8.6.1 Evaluations

Venous blood samples will be collected for measurement of plasma concentrations of macitentan and ACT-132577 at timepoints specified in the schedule of activities, see Section 1.2. Samples for sparse sampling are to be collected pre-dose and 2-10 hours post-dose.

Information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.6.2 Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of macitentan and ACT-132577 using a validated, specific, and sensitive Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) method by or under the supervision of the sponsor.

8.6.3 Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual plasma concentration-time data, using the actual sampling times (see the schedule of activities, Section 1.2), the observed analyte concentration just prior to the beginning or at the end of a dosing interval (C_{trough}) will be derived for macitentan and ACT-132577.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of macitentan and ACT-132577 will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, Creatinine Clearance, race) may be included in the model, if relevant.

Pharmacokinetic/Pharmacodynamic Evaluations

Relationships between plasma concentrations or metrics of systemic exposure and markers of pharmacological activities (ET-1 concentrations), efficacy or treatment-emergent AEs could also be explored as data allow using population approaches (eg, non-linear mixed-effects approaches).

8.7 Pharmacodynamics

Sparse venous blood samples will be collected from all participants for measurement of ET-1 at timepoints specified in the schedule of activities (see Section 1.2). Sparse sampling consists of a pre-dose and a 2-10 hours post-dose ET-1 sample.

8.8 Biomarkers

Biomarker analysis is optional for each participant. A biomarker-specific ICF should be signed prior to collection of any samples for biomarker analysis.

Blood samples for the analysis of pharmacodynamic and disease-related biomarkers can be collected at timepoints indicated in the Schedule of Activities (see Section 1.2) and archived for future analysis from all participants. No human DNA analyses will be performed on these samples.

Refer to the laboratory manual for detailed instructions for sample collection, processing and shipment of archive samples for exploratory research.

The aim of this analysis is to investigate the effect of macitentan on biomarkers involved in the pathophysiology of CTEPH. The biomarkers included in the analysis will be specified in a biomarker plan.

Refer to Appendix 3 for more information on the long-term retention of samples collected for biomarker analysis.

8.9 Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters and unscheduled visits are excluded. The data collected may be used to conduct exploratory economic analyses and will include the below data, collected from baseline up to EOS:

- Number of hospitalizations for all-cause and PH-related events.
- Number of hospital days (including duration by wards; eg, intensive care unit) for all-cause and for PH-related hospitalization.
- Number of ER visits and reason.
- Number of medical visits by specialty.

9 STATISTICAL CONSIDERATIONS

Statistical analysis will be performed by the sponsor or delegated to a Contract Research Organization under the responsibility of the sponsor. Unblinded analyses for IDMC will be performed by an independent statistician at the ISSG to prevent unblinding the sponsor (Refer to Sections 9.4.5 and 9.5). A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plans (SAP) focusing on analyses performed during a specific period (ie, IA SAP, CSR SAP part 1: DB period, CSR SAP part 2: OL period) or on individual sub-studies.

Data collected during the DB period will be summarized by intervention group and, where appropriate and applicable, compared between intervention groups with hypothesis testing. Data collected during both DB and OL extension period will be summarized overall and by intervention group assigned at the start of the DB period.

Individual listings for participant demographics, baseline characteristics and endpoint-related data will be provided as applicable and will be detailed in the SAP.

9.1 Statistical Hypotheses

9.1.1 Primary Hypothesis

The primary efficacy endpoint is the change in 6MWD from baseline to Week 28. The null and alternative hypotheses are formulated in terms of the difference between intervention groups at Week 28, as estimated from an MMRM approach utilizing all post-baseline values (Weeks 4, 8, 12, 16, 20, 24, and 28) of 6MWD changes from baseline. An MMRM model adjusted for covariates has comparable power to an ANCOVA model and intrinsically handles missing data that are not study intervention-related.

If $\mu_{MACI,28}$ and $\mu_{PBO,28}$ denote the mean changes from baseline in 6MWD at Week 28 for the participants treated with macitentan and placebo, respectively, then the following hypotheses can be considered:

$$H0: \Delta = \mu MACI,28 - \mu PBO,28 \leq 0$$
$$H1: \Delta = \mu MACI,28 - \mu PBO,28 > 0$$

The null hypothesis will be tested at a study-wise 1-sided significance level of 0.025.

The MMRM used for the primary analysis is specified in Section 9.4.1.

9.1.2 Secondary Hypotheses

The secondary endpoints will be analyzed at alpha-level governed by a predefined hierarchical testing procedure in order to maintain an overall family-wise one-sided 2.5% alpha level (Table 9).

Table 9: Secondary endpoints and associated hypotheses

Order of Secondary Endpoints	Hypotheses
1. Time to first clinical worsening (CEC confirmed) up to EODBT	The null hypothesis (H_{01}) is that there is no difference between the macitentan 75 mg and placebo survival distributions i.e., S(t) or that the difference favors placebo [H_{01}: $S_{MACI}(t) \leq S_{PBO}(t)$, $t \geq 0$]. The alternative hypothesis (H_{11}) is that there is a difference between study intervention groups in favor of macitentan 75 mg [H_{11}: $S_{MACI}(t) > S_{PBO}(t)$, $t \geq 0$].
2. Improvement (decrease) in WHO FC from baseline to Week 28 (yes/no)	The null hypothesis (H_{02}) is that the proportion of participants who improve is the same for macitentan 75 mg and placebo or is higher for placebo [H_{02}: $P_{MACI,28} \leq P_{PBO,28}$]. The alternative hypothesis (H_{12}) is that the proportion of participants who improve is higher for macitentan 75 mg [H_{12}: $P_{MACI,28} > P_{PBO,28}$].
3. Change from baseline to Week 28 in PAH-SYMPACT® symptom domains scores: 1. Cardiopulmonary 2. Cardiovascular	Separate tests will be conducted for each of the symptom domains according to the specified hierarchical order i.e., 1) Cardiopulmonary and 2) Cardiovascular. The null hypotheses (H_{03} & H_{04}) are that there is no difference between macitentan 75 mg and placebo distributions of the change from baseline to last value while on treatment up to Week 28 or that the difference is in favor of placebo [H_{03}/H_{04}: $\delta = m_{MACI,28} - m_{PBO,28} \leq 0$]. The alternative hypotheses (H_{13} & H_{14}) are that there is a difference between intervention groups in favor of macitentan 75 mg [H_{13}/ H_{14}: $\delta = m_{MACI,28} - m_{PBO,28} > 0$].

4. Change from baseline to Week 28 in EQ-5D-5L© utility score	The null hypothesis (H_{05}) is that there is no difference between macitentan 75 mg and placebo distributions of the change from baseline to last value while on treatment up to Week 28 or that the difference is in favor of placebo [H_{05}: $\delta = m_{MACI,28} - m_{PBO,28} \leq 0$]. The alternative hypothesis (H_{15}) is that there is a difference between intervention groups in favor of macitentan 75 mg [H_{15}: $\delta = m_{MACI,28} - m_{PBO,28} > 0$].
5. Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity	The null hypothesis (H_{06}) is that there is no difference between macitentan 75 mg and placebo in the proportion of time spent in moderate or vigorous physical activity or that the difference is in favor of placebo [H_{06}: $\delta = m_{MACI,28} - m_{PBO,28} \leq 0$]. The alternative hypothesis (H_{16}) is that there is a difference between intervention groups in favor of macitentan 75 mg [H_{16}: $\delta = m_{MACI,28} - m_{PBO,28} > 0$].

CEC = Clinical Event Committee ; EODBT = end of double-blind treatment; EQ-5D-5L = Euro Quality of life-5-Dimension-5-Level; PAH-SYMPACT® = Pulmonary Arterial hypertension Symptoms and Impact, WHO-FC = World health Organization Functional Class.

9.1.3 Overall Testing Strategy

This study implements a two-stage, group sequential adaptive design with one IA conducted for futility and sample size re-estimation (SSRE), with hypotheses tested at a study-wise 1-sided significance level of 0.025.

Conditional on first applying technics for controlling for type I error inflation due to performing an unblinded IA (See Section 0) and then rejecting the null hypothesis for the primary efficacy endpoint (See Section 9.1.1), the secondary efficacy endpoints are formally evaluated according to the a priori hierarchical testing order described in Section 9.1.2.

No type I error rate will be spent for the option of an early efficacy stop for futility.

9.2 Sample Size Determination

Sample size determination relies on the following assumptions:

- Targeted treatment effect (difference in changes from baseline to Week 28) = 33 m,
- Common standard deviation of change from baseline to Week 28 = 70 m

Under these assumptions, a fixed sample size of 2 × 72 participants has a power of 80% using a one-sided type I error rate of 2.5% (based on ANOVA without interim analysis).

This study implements an adaptive group sequential design with one interim analysis (see Section 9.4.5) to reassess the required sample size to maintain study power as well as to potentially prematurely stop the study for futility. A maximum of 230 participants is considered for this study based on practical considerations.

Incorporating the interim analysis and above adaptations, the global power is 89% (based on ANOVA).

9.2.1 Estimated Power for Key Secondary Endpoint: Time to Clinical Worsening

The estimated number of confirmed CW events based on different scenarios used ie, the planned number of participants (144 vs 230), accrual duration (36 m vs 57.5 m) and underlying assumption on true HR (0.4, 0.5 and 0.6) is given in Table 10. The estimated power for the key secondary

endpoint (TTCW) is presented by assuming success in primary endpoint in the hierarchical testing (HT) strategy, as well as by ignoring the HT strategy. Furthermore, the median time to CW in placebo is assumed to be 20 months and the power for the primary endpoint is assumed to be 89% (global power).

Table 10: Time to clinical worsening

True HR	Number of Participants	Accrual duration* (months)	Power HT ** (Power ***)	Number of Events	Critical value (HR)
0.60	144	36	48.1% (54.0%)	65	0.61
	230	57.5	73.8% (82.9%)	130	0.71
0.50	144	36	69.3% (77.9%)	62	0.61
	230	57.5	86.3% (97.0%)	123	0.70
0.40	144	36	83.4% (93.7%)	58	0.60
	230	57.5	88.9% (99.9%)	116	0.69

HR=Hazard Ratio, TTCW=Time to first Clinical Worsening (CEC confirmed events), HT =Hierarchical testing
* assuming a constant rate of randomization (4 participants /month). Total duration of DB period =Accrual duration + 28 weeks for the last randomized participant.
** Estimated power for the secondary endpoint (TTCW) conditional on rejecting the null hypothesis of the primary endpoint and assuming independence between primary and the secondary endpoints (i.e., Power HT= Power*89%).
*** Estimated power for TTCW, without considering HT strategy.

9.3 Populations for Analyses

For the purpose of analyses, the following populations are defined as described in Table 11.

Table 11: Overview of the different populations for analyses

Population	Description
Screened Analysis Set (SCR)	All screened participants who are assigned a participant identification number.
Full Analysis Set (FAS)	All randomized participants assigned to a study intervention. Participants will be analyzed according to the intervention they have been assigned to via IWRS.
Per-Protocol Analysis Set (PPS)	All participants included in the FAS who receive at least one dose of study intervention and who comply adequately with the protocol to be likely to exhibit the intervention effects. Criteria for sufficient compliance include exposure to treatment, availability of measurements and absence of major protocol deviations that have an impact on the treatment effect. The comprehensive list of criteria will be detailed in the SAP. Participants will be analyzed according to the intervention they are assigned to via IWRS.
Safety Analysis Set (SAS)	All participants who receive at least one dose of study intervention. Participants will be analyzed according to the intervention they actually received (which may be different to the study intervention arm they are assigned to via IWRS).
Safety Initiated Set (SIS)	All participants who initiate macitentan at any time during the DB or OL periods.
Pharmacokinetics/Pharmacodynamic (PK/PD) Analysis Set	The PK/PD analysis set is defined as participants who received at least 1 dose of study intervention and have at least 1 valid blood sample drawn for PK and/or ET-1 analysis.
PRO Analysis Sets (per PRO)	All literate participants included in the FAS for whom a suitable translation of each specific questionnaire exists. Where different from the FAS each PRO set will be defined separately.

DB = double-blind; IWRS = Interactive web response system; OL = open-label; PRO = Patient- reported outcome

The specific usage of all analysis sets is described in Table 12 and is applicable to all analysis timepoints:

- Interim analysis: when 72 participants have completed Week 28 or prematurely discontinued the study,
- Final analysis of DB period: when all participants have completed Week 28 or prematurely discontinued the study,
- Interim analysis of OL extension period: Timing is determined by the data cutoff date of the final analysis (DB period).
- Final analysis of the entire study: when all participants have completed the OL extension period.

Table 12: Analysis Sets and Their Usage at Each Analysis Timepoint

Analysis	Analysis Set					
	SCR	FAS	PPS	SAS	SIS	PK/PD
Participant disposition	X	X		X		
Description of study population		X				
Primary and secondary ** efficacy endpoints		X	X			
PK/PD endpoints						X
Exploratory efficacy endpoints**		X				
Safety endpoints				X	X*	

* For Study Closure analysis at the end of OL extension period only. ** If appropriate PRO related endpoints may use PRO Analysis Set
FAS = Full Analysis Set; OL = open-label; PPS = Per-protocol Analysis Set; SAS = Safety Analysis Set; SIS = Safety-initiated Set, PK/PD = Pharmacokinetics/Pharmacodynamic

9.4 Statistical Analyses

The statistical analysis plan (SAP-Part 1) will be based on DB treatment period. It will be finalized prior to un-blinding and will include a more technical and detailed description of the statistical analyses described in this section. SAP-Part 2 will focus on both combined DB and OL extension periods. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Unblinded IA and controlling for type I error inflation:

As the IA is planned to be performed in an unblinded manner, a statistical adjustment using inverse normal combination test will be applied to control for type I error inflation as indicated below.

For the primary endpoint analysis, two separate test statistics will be calculated. The first test statistic will be computed on all participants who already provided data for the interim analysis (Stage 1). Those who did not provide data for the interim analysis will contribute to the second test statistics irrespective of whether they were enrolled before or after the interim analysis (Stage 2). Then the two test statistics obtained from both groups of participants will be combined using the inverse normal combination method (Lehmacher 1999) with equal weights. This separation of participants in two non-overlapping groups, and the combination of the respective test statistics using prespecified equal weights ensures protection of the type I error rate.

For the key secondary endpoint time to clinical worsening (TTCW), as well as all subsequently tested secondary endpoints, the weighted combination test will be applied to control for the type I error rate inflation in context of the unblinded interim look. In addition, further protection for type I error will be envisaged by the application of an a priori hierarchical ordering.

In addition to the hypothesis testing, median-unbiased point and interval estimates for the primary and secondary endpoints will be provided based on an ordering of the sample space (Tsiatis 1987).

Further details on multiplicity testing and control for the type I error will be provided in the SAP-Part 1.

9.4.1 Primary Efficacy Analysis

The primary efficacy endpoint is change in 6MWD from baseline to Week 28.

An MMRM-based model is proposed for the primary efficacy analysis in order to use all observed values over time up to Week 28 during DB study intervention period and before rescue therapy administration. This MMRM, proposed as the primary approach, will take advantage of the longitudinal efficacy values while applying a 'penalty' to relevant intercurrent events (see attribute C for the estimand). No other penalty is imposed on discontinuations for other reasons and the values are assumed to be missing at random, as they are implicitly handled by the model. Several sensitivity and supplementary analyses will provide different perspectives and will allow the assessment of the consistency of the results.

Estimand

The estimand is described according to the following four attributes:

A. Population: Participants diagnosed with CTEPH, meeting the study eligibility criteria.

B. Variable: 6MWD changes from baseline at Weeks 4, 8, 12, 16, 20, 24, and 28.

C. Intercurrent events:

The following intercurrent events are considered:

- **Death**: A composite strategy will be used for deaths occurring up to 7 days after study intervention discontinuation without administration of rescue CTEPH therapy. All scheduled assessments following the date of death will be replaced by a 'worst-case' imputation, i.e., the sum of the participant's baseline value and the lowest observed value of 6MWD change from baseline across both treatment groups and over all assessments up to Week 28. All assessments prior to the death, as well as all imputed assessments thereafter, will be considered in the analysis
- **Premature discontinuation/Administration of rescue therapy**: A composite strategy will be employed for premature discontinuation of study intervention that are possibly treatment related (eg, clinical worsening, lack of response, adverse events, informed consent withdrawal due to tolerability issues) and/or administration of rescue CTEPH therapy (ie, associated. PH specific therapy, PEA and/or BPA procedures). All 6MWD assessment performed after end of intervention (possibly treatment related) plus 7 days or after administration of rescue therapy will be ignored in the analysis and for each visit occurring after the IE, the sum of the participant's baseline 6MWD value and the minimum of the following values: (1) the last observed value (observed 6MWD change from baseline) prior to intercurrent event at the participant level and (2) the 25^{th} percentile of observed 6MWD change from baseline values (both treatment groups pooled and over all assessments up to Week 28), will be considered instead.

D. Population-level summary:

Difference in mean 6MWD change from baseline at Week 28 between macitentan and placebo as estimated from the MMRM in the FAS (as randomized).

Statistical model

The null hypothesis will be tested by means of an MMRM. The model will include treatment (via an indicator variable for randomized intervention), time (via a categorical variable for visit), treatment-by-time interaction, one indicator variable for each stratification factor as fixed effects and baseline 6MWD as a covariable. An unstructured variance-covariance matrix will initially be specified. If convergence issues arise from the latter, a heterogeneous first-order autogressive (ARH(1)) covariance structure will be considered.

Handling of missing data

Handling of missing data arising from intercurrent events of death, premature discontinuation of study intervention, and administration of CTEPH rescue therapy are described under attribute C (above). For a given assessment, if the imputed 6MWD value results in an implausible value (ie, 6MWD <0) then the imputation of change from baseline will be capped at minus the participant's baseline value so that the imputed 6MWD value will result in a zero. ..

Missing data arising from events that are clearly not treatment-related (eg, life events such as relocation, scheduling of transportation, inadequate reimbursement of associated expenses) are assumed to be missing at random (MAR), and as such, will require no further pre-processing (ie, imputation), since the MMRM approach will implicitly impute these values.

Main analysis

The main analysis refers to the primary endpoint analysis performed when all participants have completed the 28-week DB period or prematurely discontinued the study beforehand. This analysis will be performed on the FAS.

As described in Section 0, two separate MMRMs will be computed using 6MWD data accumulated up to Week 28 from the two groups of participants: Group 1: those who participated at the IA and Group 2: those who did not participate at the IA. The resulting test statistics from the models corresponding to the two groups, denoted Z_1 and Z_2, are then combined to obtain the main test statistic Z_C by using inverse normal method (i.e., weighted Z-test) with pre specified equal weights as such $Z_C = \sqrt{0.5} \times Z_1 + \sqrt{0.5} \times Z_2$. Resulting Z_C will be compared to the standard critical value corresponding to the type I error rate of 0.025 to determine the statistical significance of the main analysis. The median-unbiased estimate of the treatment effect and the corresponding confidence interval will also be calculated. Further details will be provided in the SAP (Part 1).

In addition, the treatment effect will be estimated at 4-weekly intervals from baseline to Week 28 based on the same model along with their associated 95% CIs.

Sensitivity analyses

The following sensitivity analyses will be performed to assess the robustness of the main analysis results (normality of residuals and MAR):

- To assess the robustness of the main results regarding the underlying normality assumption of the density distribution, a rank-based analysis of covariance will be performed on 6MWD change from baseline at Week 28, using the Wilcoxon rank-based pseudo-norm (Hettmansperger 2011).

- To assess the robustness of the results of the main analysis to deviations from the MAR assumption, a tipping point analysis will be performed. For the macitentan intervention group, the missing data handled by the MMRM (see section on handling of missing data) are replaced iteratively with a range of decreasing values until the primary treatment comparison loses statistical significance. This allows quantification of the extent to which 6MWD values observed in the macitentan intervention group would have to be decreased for the results of the study to become statistically non-significant.

- Reference based analyses approaches such as Jump to reference (J2R) and Copy reference (CR) will be used to further investigate worst plausible departures from MAR for handling missing data.

- An analysis will be conducted to assess the robustness of the results of the main analysis in handling deaths occurring on/off rescue therapy in the same way so that if a participant dies while on rescue therapy the imputation rules for death will be applied.

Supplementary Analyses

In support of the primary efficacy analysis, supplementary analyses will be performed for the following supplementary estimands (see Table 13 for full definition of the estimands):

- Supplementary Estimand 1 is identical to the primary estimand but utilizes a potentially more efficient analytical approach, ie, parametric longitudinal modelling considering quadratic pattern over time.

- Supplementary Estimand 2a aims to provide results using an ANCOVA analysis on 6MWD change from baseline at Week 28, facilitating comparison of results of this study with those of the CTEPH study with macitentan 10mg (MERIT-1 study), as well as to other randomized studies with PH-approved drugs (eg, CHEST-1 for CTEPH).

- Supplementary Estimand 2b aims to provide results using MMRM as in the primary estimand while implementing a treatment policy strategy with respect to treatment discontinuations and rescue medication with a reference-based multiple imputation method for missing data. Non-parametric (Gould-type) approach will also be considered using time-to death for participants who die being ranked below all surviving participants.

- Supplementary Estimand 3 aims to provide an inferentially valid per protocol analysis to allow assessment of the treatment effect in the stratum of participants who complete the full 28-week treatment regimen without additional rescue CTEPH therapy.

Table 13: Supplementary Estimands of the Primary Endpoint

Component	Supplementary Estimand 1	Supplementary Estimand 2a	Supplementary Estimand 2b	Supplementary Estimand 3
Population	Participants diagnosed with CTEPH meeting the study eligibility criteria as randomized	Participants diagnosed with CTEPH meeting the study eligibility criteria as randomized	Participants diagnosed with CTEPH meeting the study eligibility criteria as randomized	Participants diagnosed with CTEPH meeting the study eligibility criteria who would not require rescue CTEPH therapy and who are able to complete 28 weeks of treatment
Variable	6MWD changes from baseline at Weeks 4, 8, 12, 16, 20, 24 and 28	6MWD changes from baseline at Week 28	6MWD changes from baseline at Weeks 4, 8, 12, 16, 20, 24 and 28	6MWD changes from baseline at Week 28
Intercurrent events				
Deaths occurring up to 7 days after study intervention discontinuation without administration of a rescue CTEPH therapy	Composite strategy – 'worst-case' imputation† for all post-death assessments (same as MMRM)	Composite strategy – '0' imputation for Week 28 assessment only	Composite strategy – '0' imputation up to Week 28 assessment Treatment policy – with rescue therapy	Not Applicable
Premature discontinuation of study intervention possibly treatment related	Composite: The values after premature discontinuation of study intervention plus 7 days will be imputed by the sum of the participant's baseline 6MWD value and minimum between: ' the last observed value (change from baseline) prior to intercurrent event - the 25th percentile of observed change from baseline value up to week 28 over all assessments and both treatment groups pooled	Last observation carried forward in case of missing data, values after EOT are included .	Treatment policy – values after treatment discontinuation included	Incorporated in the population definition
Administration of rescue CTEPH therapy	The values after administration of rescue therapy will be imputed by the sum of the participant's baseline 6MWD value and minimum between: ' the last observed value (change from baseline) prior to intercurrent event - the 25th percentile of observed change from baseline value up to Week 28 over all assessments and both treatment groups pooled	Treatment policy – values after rescue included	Treatment policy – values after rescue included	Incorporated in the population definition
Population-level Summary Measure	Difference in 6MWD mean change from baseline to Week 28 between macitentan and placebo as estimated from a parametric longitudinal model	Difference in 6MWD least-square mean change from baseline to Week 28 between	Difference in 6MWD mean change from baseline to Week 28 between macitentan and placebo as estimated from MMRM	Difference in 6MWD mean change from baseline to Week 28 between macitentan and placebo

Component	Supplementary Estimand 1	Supplementary Estimand 2a	Supplementary Estimand 2b	Supplementary Estimand 3
		macitentan and placebo as estimated from an ANCOVA model		
Analyses	A parametric longitudinal mixed-effects model, with a (fixed-effects) mean structure that is quadratic over time, and with a random intercept and a random slope will be considered for 6MWD changes from baseline at 4-weekly intervals up to Week 28. The model will include time, time-by-intervention interaction term, time-by-time-by-intervention quadratic interaction term, an indicator variable for each of the randomization stratification factors and the baseline 6MWD value. Random intercept and slope at the level of the participant will be considered.	An ANCOVA model, with intervention group, stratification factors and baseline 6MWD value as covariates, will be considered for 6MWD changes from baseline at Week 28. (full detail in the SAP)	MMRM model as for primary estimand. Non-parametric (Gould-type analysis)	Causal inference methods (full detail in the SAP)
Handling of missing data under MAR: missing data arising from events that are clearly not treatment-related (eg, life events such as relocation, scheduling of transportation, inadequate reimbursement of associated expenses)	Handled by the model Treatment policy – as not IE, values after end of intervention plus 7 days are included	LOCF for missing values Treatment policy – values after end of intervention are included	Referenced-based multiple imputation method such as copy reference Treatment policy – values after end of intervention plus 7 days are included	LOCF

[†]Worst-case' imputation: the sum of the participant's baseline value and the lowest observed va'ue of 6MWD change from baseline across both treatment groups and over all assessments.
6MWD = 6-minute walk distance; ANCOVA = Analysis of covariance; CTEPH = Chronic thromboembolic pulmonary hypertension; EOT = End-of-Treatment; LOCF =Last observation carried forward; MAR = Missing at random; MMRM = Mixed Model Repeated Measures; SAP = Statistical Analysis Plan.

Subgroups Analyses

In order to assess the consistency of the treatment effect across different participant subgroups for the primary efficacy variable, subgroup analyses will be performed according to the following demographic and baseline disease characteristics at randomization:

- Operability: Inoperable [including post-BPA procedure] vs persistent/recurrent after PEA surgery,
- Use of PH specific therapies at randomization: Riociguat vs other PH specific therapy vs none

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

Further subgroups will be provided in the SAP-Part 1.

9.4.2 Secondary Efficacy Endpoint Analyses

To control for multiplicity across the primary and secondary efficacy endpoints, the secondary endpoints will be analyzed hierarchically using a fixed sequence testing (see order of objectives and endpoints), at the pre-defined overall 1-sided alpha = 0.025 level of significance.

Furthermore, combination tests will be applied to each of the secondary efficacy endpoints in order to account for type I error inflation due to unblinded SSRE (See Section 0). For each of the key secondary endpoint, corresponding analysis described under "Main Analysis" will be performed separately for the two-independent group of participants (i.e., those who participated at the IA and those who did not) and resulting p values and point and interval estimates will be combined to determine the statistical significance and treatment effect.

9.4.2.1 Time to first clinical worsening up to end of double-blind treatment

The first secondary efficacy endpoint is time to first CEC-confirmed clinical worsening up to EODBT (see definition in Section 3).

Estimand

The secondary efficacy endpoint estimand follows a 'while on treatment' strategy. An event will be considered 'while on treatment' if it occurs up to 7 days after study intervention discontinuation. 7 days corresponds to the time window in which an effect can still be attributed to macitentan, based on its half-life.

The estimand is described according to the following attributes:

A. Population

Participants diagnosed with CTEPH meeting the study eligibility criteria.

B. Variable

Time (days) from randomization to first occurrence of CEC-confirmed clinical worsening up to EODBT. Only events occurring up to 7 days after study intervention discontinuation are considered.

Participants who do not experience any clinical worsening will have their time to clinical worsening right-censored at earliest among the following times and prior to first dose of OL extension intervention:

- Study intervention discontinuation (EODBT) + 7 days.
- EODBT +7 days for DB intervention completers.

C. Intercurrent events

- Not applicable

D. Population-level summary

Median time to CW and Hazard ratio of macitentan versus placebo in the FAS (as randomized).

Hypotheses:

The null hypothesis is that there is no difference between macitentan and placebo survival distributions or that the difference favors placebo. The alternative hypothesis is that there is a difference between intervention groups in favor of macitentan.

Main Analysis:

A log-rank test stratified by intervention group and randomization stratification factors will be performed in the FAS. The resulting 1-sided p-value (based on the combination test) will be compared to the nominal 1-sided type I error of 0.025.

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

T. Time to first CEC confirmed CW event (n & % by intervention group, HR, 95% CI and p value) and its components i.e., a decomposition of the first CW event (n & % by intervention group) and the first occurrence of each individual component of the CW event (n & % by intervention group, HR, 95% CI), will be presented side by side.

Stratified log rank test, Cox proportional hazards model and Kaplan Meier estimates will be used for the following exploratory analyses as appropriate. Details will be provided in SAP part 1.

Sensitivity analysis:
Time to first CEC confirmed CW event stratified by intervention group, randomization stratification factors and baseline noninvasive risk group (i.e., low, intermediate, or high).

Supportive exploratory/sensitivity analyses:

1. Time to first CEC-confirmed CW event component where each event component will be analyzed separately. Participants who do not have the relevant CEC-confirmed clinical worsening event component will have their time to clinical worsening right-censored at earliest among the following times:

    - First occurrence of any other CEC-confirmed clinical worsening event component
    - Study intervention discontinuation (EODBT)+ 7 days / prior to first dose of OL extension intervention.
    - EODBT +7 days for completers / prior to first dose of OL extension intervention.

2. Time to first "suspected clinical worsening" (SCW) with same definition as for the CEC confirmed CW endpoint but based on investigator judgment.

3. Time to first occurrence of SCW event components based on investigator judgment where each event component will be analyzed separately. Participants who do not have the relevant SCW event component will have their time to SCW right-censored at earliest among the following times:

- First occurrence of any other SCW event component
- Study intervention discontinuation (EODBT)+ 7 days / prior to first dose of OL extension intervention.

- EODBT +7 days for completers / prior to first dose of OL extension intervention.

4. Time to first occurrence of either CEC-confirmed PH-related deaths (occurring up to EODBT +7 days) or deaths occurring up to EODBT +30 days, if caused by an AE occurring up to EODBT +7 days) or unplanned PH-related hospitalization including hospitalizations for procedure due to clinical worsening (PEA/BPA) and heart/lung transplantation (up to EODBT +7 days).

5. Further exploratory analysis will be performed on CW hard endpoints such as all cause death and all cause hospitalization occurring over the combined DB and OL periods. In case of heterogeneity in the treatment effect due to informative censoring caused by competing risk between components and the subsequent switch to OL macitentan 75 mg from DB placebo group, the SAP (Part 2) will describe methods such as rank preserving structural failure time models, marginal structural models and indirect comparisons to external control arms, to estimate the unbiased treatment effect.

9.4.2.2 Improvement in WHO FC from baseline to last value while on treatment up to Week 28 (yes/no)

Endpoint definition

Improvement (decrease) in WHO FC from baseline to Week 28 will be calculated for each participant.

For consistency with the primary 6MWD estimand:

- For deaths occurring up to 7 days after study intervention discontinuation without administration of rescue CTEPH therapy, all scheduled assessments following the date of death will be imputed by a 'worst-case' imputation (WHO FC=IV). All assessments prior to the death, as well as all imputed assessments thereafter, will be considered in the analysis.
- Assessments that are after (possibly treatment related) discontinuation of study intervention + 7 days and/or administration of rescue CTEPH therapy are excluded from the analysis. The sum of the participant's baseline WHO FC score and the 75th percentile (from observed WHO FC change from baseline across both treatment groups and over all assessments) will be imputed to Week 28 following these intercurrent events.

Missing values at Week 28 (for reasons other than described above) will be imputed by carrying forward the last assessment before discontinuation of study intervention + 7 days and/or administration of rescue CTEPH therapy.

Hypotheses

The null hypothesis is that the proportion of participants who improve is the same for macitentan and placebo or is higher for placebo. The alternative hypothesis is that the proportion of participants who improve is higher for macitentan.

Main Analysis

The data in the FAS will be analyzed by a Cochran-Mantel-Haenszel test adjusted by WHO FC at baseline, intervention group, and randomization stratification factors. The resulting p-value will be compared to the nominal 1-sided type I error of 0.025.

9.4.2.3 Change from baseline to last value while on treatment up to Week 28 in PAH-SYMPACT®

Endpoint definition

The change from baseline to last value while on treatment up to Week 28 will be calculated for each participant and for each domain (cardiopulmonary symptoms and cardiovascular symptom). Separate tests will be conducted for each domain according to the above hierarchical order.

Hypothesis

The null hypothesis is there is no difference between macitentan and placebo distributions of the change from baseline to last value while on treatment up to Week 28 or that the difference is in favor of placebo. The alternative hypothesis is that there is a difference between intervention groups in favor of macitentan.

Main Analysis

The change from baseline to last value while on treatment up to Week 28 will be analyzed by means of non-parametric Mann-Whitney U test in the FAS. A point estimate for the placebo corrected location shift will be displayed along with associated 95% CI and p-value using the Hodges-Lehmann method. The resulting p-value from the U statistic will be compared to the nominal 1-sided type I error of 0.025.

For consistency with the primary 6MWD estimand:

- For deaths occurring up to 7 days after study intervention discontinuation and without administration of a rescue CTEPH therapy, all scheduled assessments following the date of death will be imputed by a 'worst-case' imputation, ie, the sum of participant's baseline value and the highest observed value of change from baseline across both treatment groups and over all assessments. All assessments prior to the death, as well as all imputed assessments thereafter, will be considered in the analysis.
- Assessments that are after possible treatment related discontinuation of study intervention + 7 days and/or administration of rescue CTEPH therapy are excluded from the analysis. The sum of the participant's baseline value and the maximum of the following values: (1) the last observed value (change from baseline) prior to intercurrent event at the participant level and (2) the 75^{th} percentile of observed change from baseline values (both treatment groups pooled and over all assessments) will be imputed to Week 28 following these intercurrent events.

For Week 28 assessments that are missing for other reasons, assessments will be imputed by LOCF.

9.4.2.4 Change from baseline to last value while on treatment up to Week 28 in EQ-5D-5L© utility score

Endpoint definition

The change from baseline to last value while on treatment up to Week 28 will be calculated for each participant. Utilities will be calculated according to the crosswalk algorithm developed by the EuroQoL group (Van Hout 2012) in order to follow the NICE position paper (NICE 2018), ie, EQ-5D-5L© values will be mapped into the 3L values for analysis.

Hypotheses

The null hypothesis is there is no difference between macitentan and placebo distributions of the change from baseline to last value while on treatment up to Week 28 or that the difference is in favor of placebo. The alternative hypothesis is that there is a difference between intervention groups in favor of macitentan.

Main Analysis

The analysis will follow the same principles as for the PAH-SYMPACT® in the FAS.

9.4.2.5 Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity

Endpoint definition

For each scheduled visit, the 14 days prior to the visit will be considered as the assessment period for physical activity. To be considered evaluable for a given time, actigraphy variables should have been measured for at least 7 complete days (consecutive or not) at a specific time period of assessment (baseline, and 4-weekly intervals up to Week 28). A complete day is defined as a record of at least 7 waking hours of data. During these periods, the time spent in different level of activity: sedentary/light/moderate/vigorous will be determined based on activity counts per minutes and expressed as proportion relative to the period duration. The categories moderate and vigorous will be combined for the analysis and will represent the proportion of time spent in moderate to vigorous physical activity.

At each visit, the proportion of time spent in moderate to vigorous activity will be estimated.

For consistency with the primary 6MWD estimand:

- For deaths occurring up to 7 days after study intervention discontinuation without administration of rescue CTEPH therapy, all scheduled assessments following the date of death will be imputed by a 'worst-case' imputation (proportion of time spent equal to 0). All assessments prior to the death, as well as all imputed assessments thereafter, will be considered in the analysis.
- Assessments that are after (possibly treatment related) discontinuation of study intervention + 7 days and/or administration of rescue CTEPH therapy are excluded from the analysis. The sum of the participant's baseline value and the minimum of the following values: (1) the last observed value (change form baseline) prior to intercurrent event at the participant level and

(2) the 25th percentile of observed change from baseline values (both treatment groups pooled and over all assessments) will be imputed to Week 28 following these intercurrent events.

Week 28 assessments that are missing for other reasons will be imputed by carrying forward the last observed value before discontinuation of study intervention + 7 days and/or administration of rescue CTEPH therapy (LOCF).

The change from baseline to last value while on treatment up to Week 28 will be calculated for each participant for the accelerometry-assessed proportion of time spent in moderate to vigorous physical activity. Each physical activity level will be determined based on activity counts per minutes.

Hypothesis

The null hypothesis is there is no difference between macitentan and placebo in the proportion of time spent in moderate to vigorous physical activity or that the difference is in favor of placebo. The alternative hypothesis is that there is a difference between intervention groups in favor of macitentan.

Main Analysis

The data in the FAS will be analyzed by an ANCOVA adjusting for baseline actigraphy value and randomization stratification factors. The resulting p-value will be compared to the nominal 1-sided type I error of 0.025.

The above approach assumes that the proposed actigraphy endpoint will be approximately normally distributed. The residuals from the ANCOVA will be tested for normality using the Shapiro-Wilk test. Should this be significant at the 5% level, a non-parametric approach will be used (stratified Wilcoxon test).

9.4.3 Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are AEs with onset during the intervention period or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

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

Summaries for the DB period will be by study intervention (macitentan or placebo) and will include all events up to the start of OL period, or up to 30 days after study intervention discontinuation, whichever occurs first.

The AEs of special interest will be defined in the SAP.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint by intervention group. Frequency tabulations of the abnormalities will be made.

Vital Signs

Descriptive statistics of pulse rate, SBP and DBP values and changes from baseline will be summarized at each scheduled timepoint by intervention group.

9.4.4 Other Analyses

Pharmacokinetic Analyses

If feasible, population PK analysis of plasma concentration-time data of macitentan may be performed using nonlinear mixed-effects modeling. Data may be combined with other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Relationships between plasma concentrations or metrics of systemic exposure and markers of pharmacological activities, efficacy or treatment-emergent adverse events could also be explored as data allow using population approaches (eg, non-linear mixed effects approaches). For example, Pharmacokinetic-ET-1 relationships will be explored.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for macitentan and its active metabolite ACT-132577 and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available plasma concentrations of macitentan and ACT-132577 per intervention group. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

For each intervention group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of macitentan and ACT-132577.

Exploratory Analyses

Analysis of the exploratory variables will be described in the SAP.

Descriptive /sensitivity analyses will be performed to evaluate the impact of COVID-19 pandemic on the efficacy and safety endpoints. Details will be provided in the SAP -Part 1.

9.4.5 Interim Analysis

The proposed study design consists of a two-stage, group sequential, adaptive design. The "adaptive" aspect of this study focusses either on the early termination of the study for futility or performing an unblinded SSRE. One unblinded interim analysis is planned once a total of 72 sequentially randomized participants have completed Week 28 or prematurely discontinued the study.. This gives an information fraction of

$$t_1 = {}^{72}/_{144} = 0.50$$

At the time of the IA data cut-off, all available data including those from ongoing participants not having yet completed Week 28 but are having at least one 6MWD assessment on 75 mg maintenance dose will be considered to perform the SSRE. Based on the details provided in the IDMC charter, ISSG will develop an IA SAP before performing any unblinding for the futility analysis and SSRE.

At the interim analysis, the following decisions may be taken:

- Prematurely stop the study for futility
- Maintain the sample size ie, 144 participants
- Increase the sample size for the second stage of the study up to a maximum of 230 participants.

An IDMC will be established as described in Section 9.5.

The IDMC will review the results of the interim analysis and periodic safety analyses performed by the ISSG and will provide corresponding recommendations to the sponsor in line with the IDMC charter. The sponsor will decide whether to take these recommendations into account.

The IDMC may recommend continuing the trial to its planned end, even if an interim stopping criterion is statistically met. This applies to futility stopping criterion.

9.5 Data Monitoring Committee

An **Independent Data Monitoring Committee (IDMC)** has overall responsibility for safeguarding the interests of participants by monitoring safety and efficacy data obtained during

the study and for reviewing the results of the interim analysis. The IDMC will make appropriate recommendations based on all the reported data and statistical analysis prepared by an independent statistician at the Independent Statistical Support Group (ISSG), thereby ensuring that the study is conducted in accordance with the highest scientific and ethical standards. All communication between the IDMC and the Sponsor will be directed through the Sponsor Committee, which includes senior medical and statistical members. Due to the adaptive nature of the trial, clear and protected communication flows will be established. Details on IDMC roles, responsibilities and operating procedures are provided in the IDMC Charter. The IDMC will be fully operational prior to enrollment of the first participant into the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
AC	Adjudication committee
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARH(1)	Heterogeneous first-order autogressive
AST	Serum aspartate aminotransferase
AUC	Area under the curve
BPA	Balloon pulmonary angioplasty
CEC	Clinical event committee
CI	Cardiac index
CL	Confidence limit
C_{max}	Maximum plasma concentration
CO	Cardiac output
CRF	Case report form(s) (paper or electronic as appropriate for this study)
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiogram
CYP	Cytochrome
DB	Double-blind
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DHT	Dihydrotestosterone
dPAP	Diastolic pulmonary artery pressure
dSAP	Diastolic systemic arterial pressure
ECG	Electrocardiogram
eDC	Electronic data capture
EMA	European Medicines Agency
EODBT	End-of-DB treatment
EOLT	End of open-label treatment
EOS	End of study
EQ-5D-5L©	Euro Quality of life-5-Dimension-5-Level
ER	Emergency room
ERA	Endothelin receptor antagonist
ET	Endothelin receptor
FC	Functional class
FEV_1/FVC	Forced expiratory volume in 1 second / forced vital capacity
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HAESI	Serious hepatic adverse events of special interest
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference for Harmonisation
IDMC	Independent Data Monitoring Committee
IE	Intercurrent events
IEC	Independent Ethics Committee
ILSDRB	International Liver Safety Data Review Board
IND	Investigational New Drug
IRB	Institutional Review Board
ISSG	Independent Statistical Support Group
IWRS	Interactive web response system
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/Mass Spectrometry

LH	Luteinizing hormone
LLN	Lower limits of normal
LOAEL	Lowest-observed-adverse-effect level
LVEDP	Left ventricular end diastolic pressure
MAR	Missing at random
MCT	Monocrotaline
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
mPAP	Mean pulmonary arterial pressure
mPAWP	Mean pulmonary arterial wedge pressure
MRA	Magnetic resonance angiography
mRAP	Mean right atrial pressure
mSAP	Mean systemic arterial pressure
NT-proBNP	N-terminal prohormone of Brain natriuretic peptide or N-terminal pro B-type natriuretic peptide
Od	Once daily
OL	Open-label
PA	Pulmonary angiography
PAH	Pulmonary arterial hypertension
PAH-SYMPACT®	Pulmonary Arterial Hypertension - Symptoms and Impact
PAWP	Pulmonary artery–wedge pressure
PD	pharmacodynamic(s)
PDE-5	Phosphodiesterase type-5
PEA	Rescue pulmonary endarterectomy
PFT	Pulmonary function test
PGA-S	Patient Global Assessment of Severity
PH	Pulmonary hypertension
PHQ-8	Patient Heath Questionnaire
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PQC	Product Quality Complaint
PR	Pulse rate
PRO	Patient-reported outcome(s) (paper or electronic as appropriate for this study)
PTOP	Post-treatment observation period
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RV	Right ventricular
RVSP	Right ventricular systolic pressure
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCW	Suspected clinical worsening
SF36	36-item Short Form survey
SoA	Schedule of Activities
sPAP	Systolic pulmonary artery pressure
sSAP	Systolic systemic arterial pressure
SSRE	Sample size re-estimation
SUSAR	Suspected unexpected serious adverse reaction
SvO_2	Mixed venous oxygen saturation
t½	Half-life
TPR	Total pulmonary resistance
ULN	Upper limit of normal
V/Q	Ventilation / Perfusion
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI©: GH	Work Productivity and Activity Impairment Questionnaire©: General Health

Definitions of Terms

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

10.2 Appendix 2: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit
INR</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose [nonfasting]
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)</td><td>Total and direct bilirubin
Alkaline phosphatase
Uric acid
Calcium
Phosphate
Albumin
Total protein
Magnesium
Thyroid stimulating hormone, TSHIron
Ferritin</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping/temporary interruption criteria and required actions and follow-up assessments are given in Section 7.1.</td></tr>
<tr><td>Pregnancy tests (women of child-bearing potential only)</td><td colspan="3">• A serum pregnancy test will be performed at each regular site visit.
• A urine pregnancy test must be performed in between visits on a monthly basis if the interval between regular visits exceeds 1 month</td></tr>
</table>

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)

- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

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

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

INFORMED CONSENT PROCESS

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

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

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

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 90 days from the previous ICF signature date.

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

DATA PROTECTION

Privacy of Personal Data

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

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

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

Exploratory PK, pharmacodynamic and biomarker research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand macitentan, to understand CTEPH, to understand differential intervention responders, and to develop tests/assays related to macitentan and CTEPH. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal from the Use of Research Samples).

COMMITTEES STRUCTURE

Data Monitoring Committee

Refer to Section 9.5

Adjudication Committee (AC)

An Adjudication Committee, which is composed of CTEPH experts, will assess operability of participants and confirm their eligibility for participation in the study. The committee will review predefined data for all participants during the screening period and assess whether the participants are technically inoperable or have persistent/recurrent CTEPH. The composition and functioning of the AC is described in the AC charter.

Clinical Event Committee (CEC)

A Clinical Event Committee (CEC) will review and adjudicate in a blinded fashion each clinical worsening event and the time of its first occurrence. In addition, primary reason for hospitalization and mode of death, will be adjudicated. A case narrative any other relevant supporting information (hospital discharge summaries, local laboratory or imaging data, etc.) must be provided to the CEC. Full details for this procedure, as well as the composition and operation of the CEC is described in the CEC charter.

Steering Committee (SC)

A Steering Committee is involved in the study design and will be consulted prior to and during the study for relevant medical issues and study publications.

Independent Liver Safety Data Review Board (ILSDRB)

An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) has been appointed to provide ongoing assessment and advice regarding hepatic AEs of special interest that require further evaluation during the study as per the ILSDRB charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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

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

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been

submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of ECG and PRO - and possibly 6MWT data, as well as clinical laboratory data from a central laboratory, into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

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

CASE REPORT FORM COMPLETION

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

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

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

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

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

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

SOURCE DOCUMENTS

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

The author of an entry in the source documents should be identifiable.

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

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

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

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

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for

use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

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

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

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

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

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

ON-SITE AUDITS

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

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

RECORD RETENTION

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

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

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

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

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

Study Termination

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

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

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

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

10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

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

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

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

Serious Adverse Event

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

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated with the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is related by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator based on medical judgment. The following selection should be used to assess all adverse events (AE).

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study intervention administered and reported as either related or not related. The determination of the likelihood that the study intervention caused the AE will be provided by the investigator.

Related

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

Not Related

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

SEVERITY CRITERIA

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

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

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

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

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

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

PROCEDURES

All Adverse Events

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

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

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

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Follow-up information about a previously reported SAE must also be reported to the sponsor within 24 hours of receiving it. Sponsor personnel may contact the investigator to obtain further information. The follow-up information obtained after the participant's EOS visit (see Section 4.4) must be reported to the sponsor but is not recorded in the eCRF.

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for a part of the intervention period.

The cause of death of a participant in a study within 4 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

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

Procedures

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

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

Contacting Sponsor Regarding Product Quality

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

10.5 Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.4, Pregnancy and Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

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

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

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Acceptable methods of contraception:

Option 1	OR	Option 2	OR	Option 3	OR	Option 4
One method from this list		**One method from this list**				
• Tubal sterilization (occlusion or ligation of tubes at least 6 weeks prior to screening), • Implantable# hormonal contraceptives • Intrauterine devices		• Oral, • Transdermal#, or • Injectable# hormonal contraceptives		• Sterilization of the male partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate		• True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the participant.
		PLUS one method from this list • Diaphragm*#, • female condom*# • cervical cap*#, • partner's use of a condom*		**PLUS one method from this list** • Oral, • Implantable#, • Transdermal#, or • Injectable# hormonal contraceptives • Intrauterine devices • Diaphragm*#, • female condom*# • cervical cap*#, • partner's use of a condom*		

*used in combination with a spermicide, unless unavailable locally.
#methods that are not approved/certified for use in Japan.

10.6 Appendix 6: Child-Pugh Score

Clinical and Lab Criteria	**Points**		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3
Child-Pugh class obtained by adding score for each parameter (total points): Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease Class C = 10 to 15 points (most severe liver disease)			

10.7 Appendix 7: Sponsor 6-minute Walk Test Guidance

This document stipulates the criteria under which study-required 6MWTs will be carried out in Clinical Protocol 67896062CTP3001 (Amendment 4).

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

1. INSTRUCTIONS

General

- The 6-Minute Walk Test (6MWT) must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track length for the 6MWT must be free of obstacles. The use of treadmill and a continuous course, eg, a circuit, is not allowed.

- The ideal track length used for the 6MWT is 30 meters (If the track is shorter, it must be no shorter than 20 meters in length). The track must be marked at regular intervals to facilitate measurement of the distance walked (markings every 3 meters are recommended). The turnaround points must be marked with a cone. A starting line, which marks the beginning and the end of each lap (one lap is twice the length of the track used at the site), needs to be marked on the floor.

- Local safety practice regarding medical emergencies and contraindications for 6MWT must be followed at each participating site.

- The person administering the 6MWT (tester) needs to stand near the starting line during the 6MWT and must not walk with the participant, and not get distracted during the conduct of this 6MWT (eg, by talking to someone).
- Rest periods are allowed if the participant can no longer continue. If the participant needs to rest, he/she may pause, lean against the wall and continue walking whenever he/she feels able. The timer must continue to run even if the participant stops to rest. The 6MWT can be stopped at any moment as due to medical emergencies or safety issues such as chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance
- The 6MWT is a non-encouraged test. An even tone of voice must be used when using the standard phrases. No other instructions or words of encouragement are given during the test, other than the pre-scripted phrases (see instructions to participant). Eye contact and body language signaling the participant to speed up must be avoided during the test.
- Whenever possible, for an individual participant, repeat 6MWTs must be conducted in the same corridor and by the same tester, and preferably at about the same time of the day (ie, within ± 2 hours of the baseline test) to minimize variability.
- If a participant is oxygen dependent, the flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT. Additionally, the way oxygen is delivered (delivery device, application route, way of carrying

delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.

Training tests

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

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

Timing

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

2. TEST REQUIREMENTS

Participant

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

Equipment to perform the test

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

3. PERFORMING THE 6MWT

Assessments before the 6MWT

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

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

Then, the tester will ask:

– *"Please grade your level of exertion using this scale.*

Record the baseline-6MWT dyspnea and level of exertion using the Borg CR10 scale® on the 6MWT worksheet.

Instructions to the participant during the 6MWT

The tester uses the following exact dialogue with the participant:

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

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

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

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

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

"Start now, or whenever you are ready"

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

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

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

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

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

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

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

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

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

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

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

When the timer alarm rings the tester says:

"Stop!"

Assessments after the 6MWT

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

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

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

Then, the tester will ask:

- *"Please grade your level of exertion using this scale.*

The tester will record the post-6MWT dyspnea and level of exertion on the 6MWT worksheet.

4. 6MWT WORKSHEET

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

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

10.8 Appendix 8: Borg CR10 Scale®

Instructions for use of the Borg CR10 Scale®

The Borg CR10 Scale® will be explained in detail to the participants at Screening before starting the first 6MWT (questionnaires and instructions will be provided in local language).

The tester will provide the following instruction to the participant:

"Use this rating scale to report how strong your perception of dyspnea and level of exertion is. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or "Extremely strong", "Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". If your feeling is "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", - "Extremely strong", "Maximal" – you can use a larger number, eg, 12 or still higher (that's why "Absolute maximum" is marked with a dot "•").

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating dyspnea[a] give a number that corresponds to how hard and strenuous you perceive your breathing to be. The perception of dyspnea is mainly the feeling that one cannot breathe well enough.

0 - "Nothing at all", means that you don't feel any shortness of breath.

1 - "Very weak" means a very light shortness of breath.

3 - "Moderate" is somewhat but not especially hard. You are somewhat shorter of breath.

5 - "Strong". Breathing is getting difficult. The effort to breathe is about half as intense as "Maximal".

7 - "Very strong" is quite strenuous. You can still breathe, but breathing is getting very difficult.

10 - "Extremely strong – Maximal" is the greatest shortness of breath you have ever experienced in your life.

"•" - Is "Absolute maximum" for example "12" or even more.

[a] The instructions for rating dyspnea have been customized by the sponsor based on the instructions for rating exertion. These modifications have not been validated by Borg Perception AB.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 - “Nothing at all”, means that you don’t feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 - “Very weak” means a very light exertion. As taking a shorter walk at your own pace.

3 - “Moderate” is somewhat but not especially hard. It feels good and not difficult to go on.

5 - “Strong”. The work is hard and tiring, but continuing isn’t terribly difficult. The effort and exertion is about half as intense as “Maximal”.

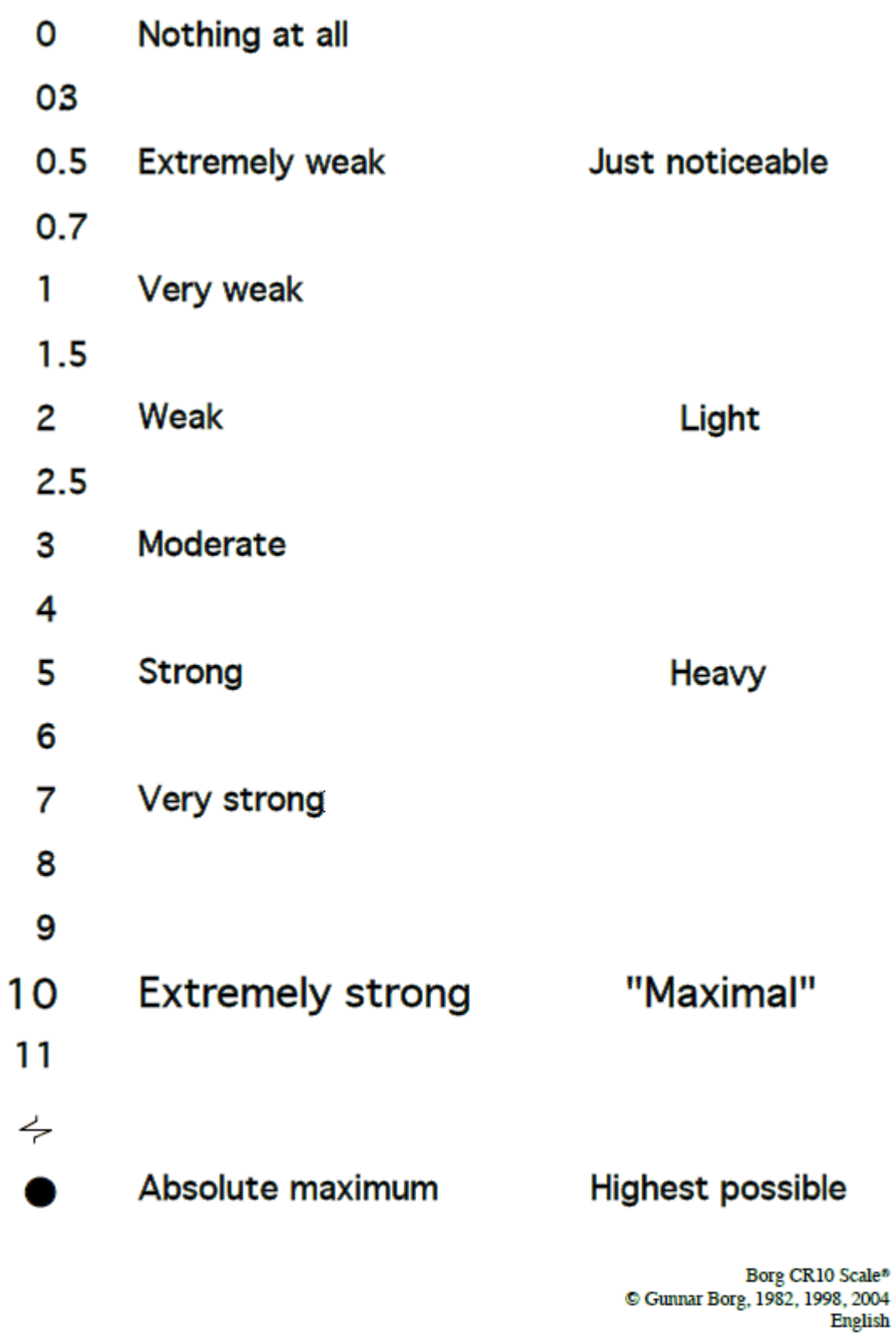
7 - “Very strong” is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 - “Extremely strong – Maximal” is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

“•” - Is “Absolute maximum” for example “12” or even more.

Any questions?”

Borg CR10 Scale®:



10.9 Appendix 9: WHO Function Classification of Pulmonary Hypertension

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

10.10 Appendix 10: PAH-SYMPACT® Questionnaire

1. Administration and Scoring

1.1 Administration

The PAH-SYMPACT® is composed of two parts: the Symptoms part, which is administered daily for seven days, and the Impacts part, which is administered once at the end of the seven-day administration period. The PAH-SYMPACT® has been used in both an electronic patient-reported outcome and a paper-pencil format.

The Symptoms part contains 11 symptom items across two domains plus one question about oxygen use. There is no total symptom score; the two domains are: Cardiopulmonary Symptoms and Cardiovascular Symptoms. The question on oxygen use stands on its own and is not used as part of the domain scores. Symptoms items have a recall period of "today," and it is recommended that the questions be completed in the evening. As symptoms vary by day, the Symptoms part should be completed daily over seven consecutive days.

The Impact part contains 11 items across two domains: Physical Impacts and Cognitive/Emotional Impacts. Impact items have a recall period of the last week; hence, the questions should be completed on the seventh day of the seven-day administration period of the Symptoms part.

1.2 Scoring

Items have a five-point Likert response scale; responses are transcribed to numerical values for further analyses.

Pulmonary **A**rterial **H**ypertension-**Sym**ptoms and Im**pact (PAH-SYMPACT**® Questionnaire

Programming note: Day 1 (First day of diary completion- Symptoms items only)

INSTRUCTIONS

Each day you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms.**

On the 7th day you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

Programming note: Days 2-6 (Subsequent days prior to last day in week- Symptoms items only)

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms.**

Please do not skip any questions. There are no right or wrong answers to any of the questions.

Programming note: Day 7 (Last day of week- Symptoms and Impact items)

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

SYMPTOMS

1. In the past 24 hours …

   Did you use oxygen?
   ☐0 No
   ☐1 Yes If yes: How many hours? _____

Answer the questions that follow based on your experiences **regardless of whether you were using oxygen or not.**

2. In the past 24 hours …

   How would you rate your **shortness of breath**?
   ☐0 No shortness of breath at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

3. In the past 24 hours …

   How would you rate your **fatigue**?
   ☐0 No fatigue at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

4. In the past 24 hours …

   How would you rate your **lack of energy**?
   ☐0 No lack of energy at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

5. In the past 24 hours …

   How would you rate the **swelling in your ankles or legs**?
   ☐0 No swelling in ankles or legs at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

6. In the past 24 hours …

   How would you rate the **swelling in your stomach area**?
   ☐0 No swelling in stomach area at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

7. In the past 24 hours …

   How would you rate your **cough**?
   ☐0 No cough at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

8. In the past 24 hours …

   How would you rate your **heart palpitations (heart fluttering)**?
   ☐0 No heart palpitations (heart fluttering) at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

9. In the past 24 hours …

   How would you rate your **rapid heartbeat**?
   ☐0 No rapid heartbeat at all
   ☐1 Mild
   ☐2 Moderate
   ☐3 Severe
   ☐4 Very Severe

10. In the past 24 hours …

    How would you rate your **chest pain**?
    ☐0 No chest pain at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

11. In the past 24 hours …

    How would you rate your **chest tightness**?
    ☐0 No chest tightness at all
    ☐1 Mild
    ☐2 Moderate
    ☐3 Severe
    ☐4 Very Severe

12. In the past 24 hours …

How would you rate your **lightheadedness**?
☐0 No lightheadedness at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

IMPACTS

For the following questions, please select the answer that best describes how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS.** Answer the questions based on your experiences regardless of whether you were using oxygen or not.

1. In the past 7 days …

   Were you able to **walk slowly on a flat surface**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

2. In the past 7 days …

   Were you able to **walk quickly on a flat surface**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

3. In the past 7 days …

   Were you able to **walk uphill**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

4. In the past 7 days …

   Were you able to **carry things**, such as bags or baskets?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

5. In the past 7 days …

   Were you able to **do light indoor household chores**, such as preparing food, cleaning surfaces, or tidying up?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

6. In the past 7 days …

Were you able to **wash or dress yourself**?
☐0 Yes, with no difficulty at all
☐1 Yes, with a little difficulty
☐2 Yes, with some difficulty
☐3 Yes, with much difficulty
☐4 No, not able at all

7. In the past 7 days …

How much did you **need help from others**?
☐0 Not at all
☐1 A little bit
☐2 Some
☐3 Quite a bit
☐4 Very much

8. In the past 7 days …

Were you able to **think clearly**?
☐0 Yes, with no difficulty at all
☐1 Yes, with a little difficulty
☐2 Yes, with some difficulty
☐3 Yes, with much difficulty
☐4 No, not able at all

9. In the past 7 days …

How **sad** did you feel?
☐0 Not at all
☐1 A little bit
☐2 Somewhat
☐3 Very
☐4 Extremely

10. In the past 7 days …

How **worried** did you feel?
☐0 Not at all
☐1 A little bit
☐2 Somewhat
☐3 Very
☐4 Extremely

11. In the past 7 days …

How **frustrated** did you feel?
☐0 Not at all
☐1 A little bit
☐2 Somewhat
☐3 Very
☐4 Extremely

10.11 Appendix 11: 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L©)

CCI

[redacted]

Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*

EQ-5D-5L© VAS Scale

CCI

CCI

CCI

10.12 Appendix 12: Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

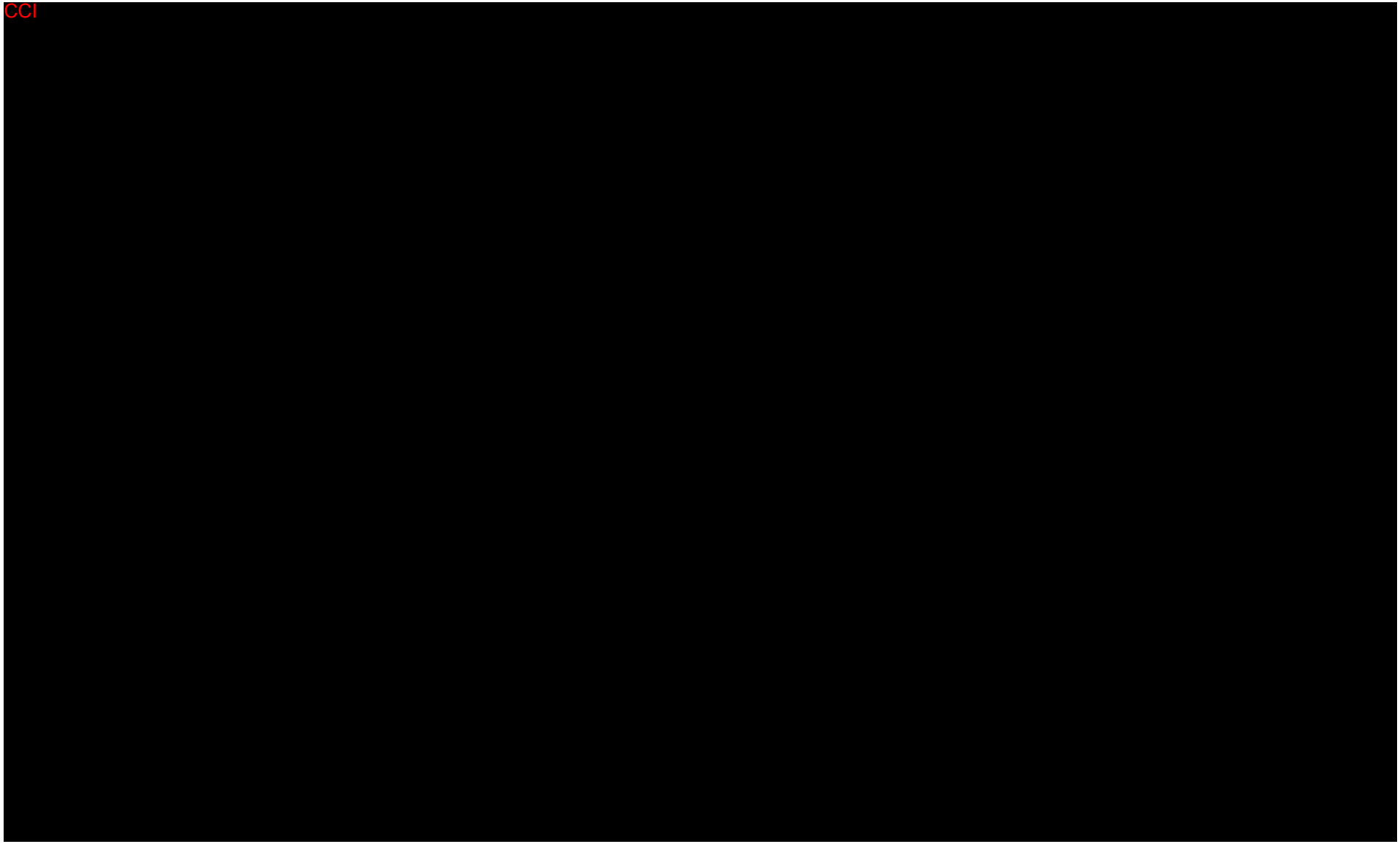
By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

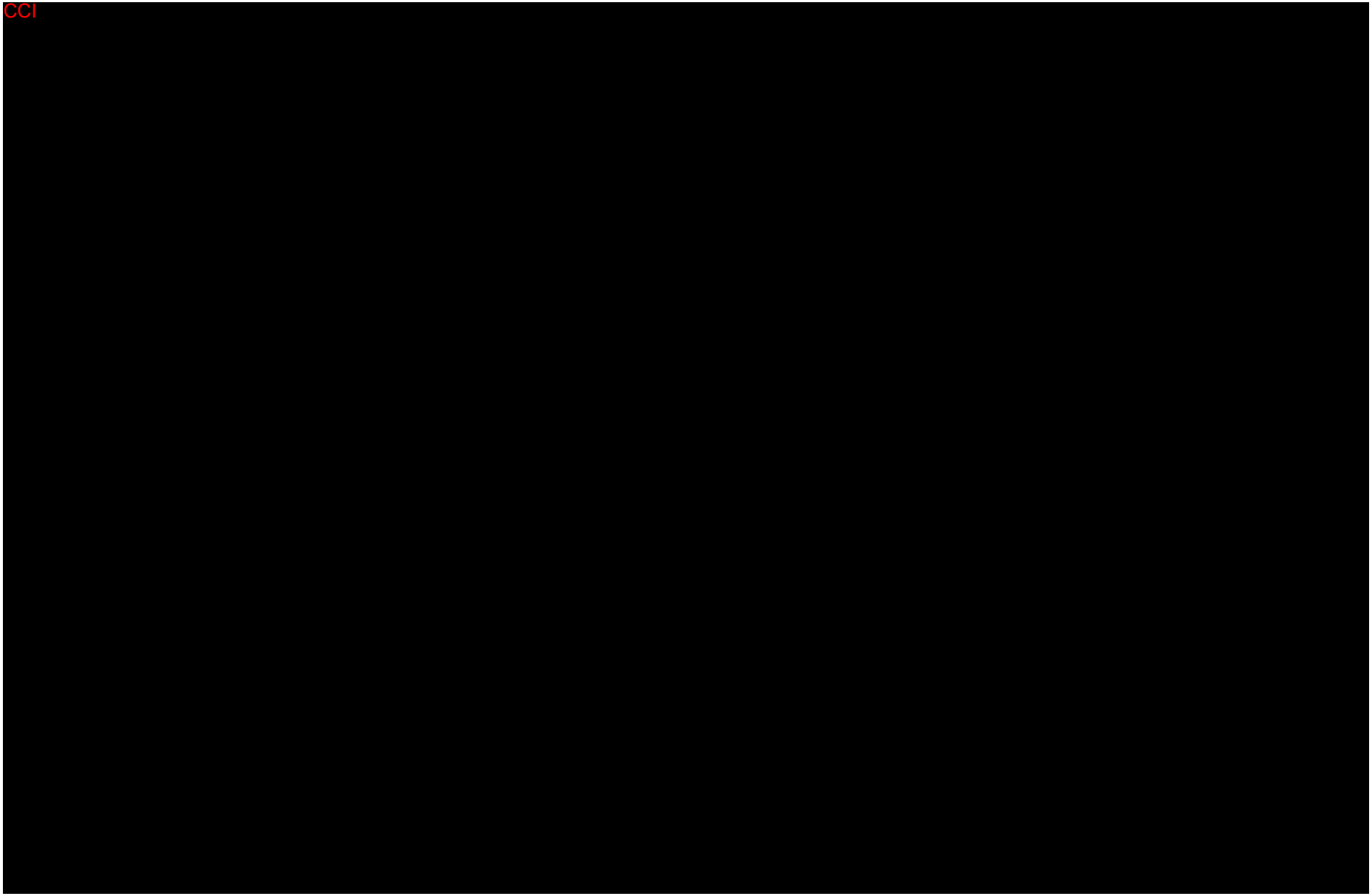
Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

10.13 Appendix 13: SF-36®v2 Health Survey Single-Item Presentation Text Acute, United States (English)




CCI


CCI

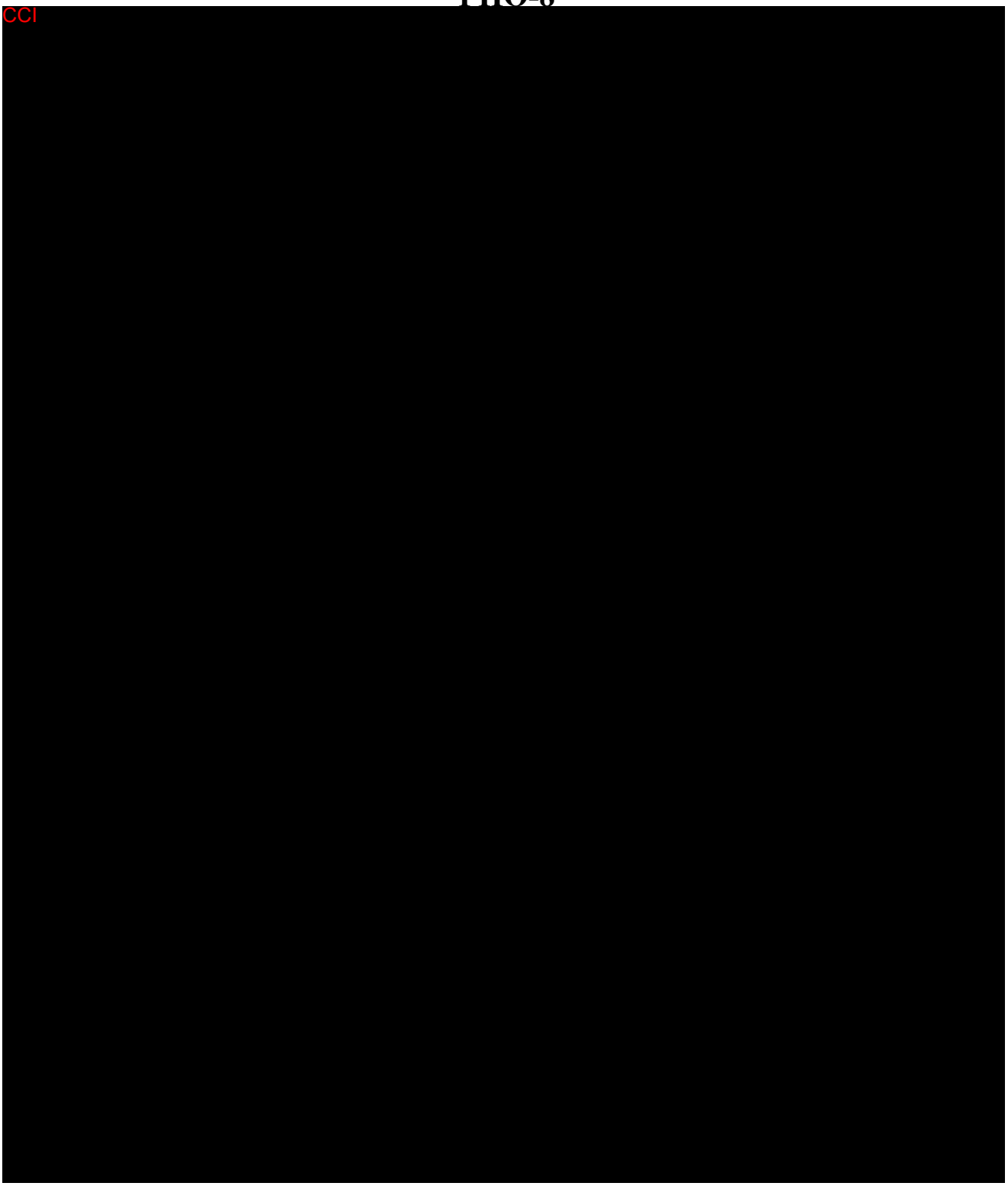
CCI

(SF-36v2® Health Survey Acute, United States (English)

10.14 Appendix 14: Patient Health Questionnaire (PHQ-8)

PHQ-8

CCI



10.15 Appendix 15: Patient Global Assessment of Severity (PGA-S)

Patient Global Assessment of Disease Severity (PGA-S)

This question refers to symptoms related to chronic thromboembolic pulmonary hypertension. Please choose the response that best describes the severity of your symptoms today. (Check one response)

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

10.16 Appendix 16: Actelion Heart Catheterization Guidance

ACTELION HEART CATHETERIZATION GUIDANCE WHEN HEMODYNAMIC VARIABLES ARE ENDPOINTS

- This guidance only applies to participants who will require a baseline and a post-baseline right heart catheterization (RHC) with/without a left heart catherization (LHC) (if needed). This guidance does not apply to RHC/LHC used only for participant eligibility.

- Hemodynamic evaluations will be carried out according to this guidance for those conditions and hemodynamic parameters that are described below. Further hemodynamic evaluations will be carried out according to the catheterization laboratory's local practice.

1. HEART CATHETERIZATION PROCEDURES

1.1 Conditions

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

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

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

1.2 'Zeroing'

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

1.3 Oxygen

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

2. HEART CATHETERIZATION MEASUREMENTS

2.1 Right Heart Catheterization measurements

- **Pulmonary Artery pressure (PAP)**

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

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

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

- **Pulmonary artery wedge pressure (PAWP)**

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

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

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

- **Cardiac Output**

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

If **thermodilution method** is used:

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

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

- Only 1 value is required and must be documented in the source notes.

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

2.2 Left Heart Catheterization measurement

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

2.3 Other measurements

RAP, dSAP, sSAP, SVO_2 are measured as per local practice.

3. DOCUMENTATION

3.1 Tracings

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

3.2 Heart catheterization worksheet

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

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

10.17 Appendix 17: Guidance on Male Reproductive System Safety Sub-study

1. BACKGROUND AND RATIONALE

Animal data on macitentan indicate a risk on the male reproductive system, structure and function. These findings consist mainly of morphological changes in the testes including tubular dilatation and, at higher doses, tubular degeneration and hypospermatogenesis. These effects were reversible and did not impact reproductive variables such as mating, fertility and fecundity. The relevance of these findings to humans is unknown (Macitentan IB).

Macitentan, like other endothelin receptor antagonists (ERAs), may have an adverse effect on spermatogenesis, and decrease in sperm count in humans cannot be excluded.

This sub-study is conducted to provide additional safety data of chronic treatment with macitentan 75 mg on testicular function in patients with PAH and CTEPH.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Exploratory	
To evaluate the effect of chronic administration of macitentan 75 mg on semen parameters in male participants	Percent changes from baseline to Week 24* in: • semen volume • sperm concentration • sperm motility • sperm morphology
To evaluate the effect of chronic administration of macitentan 75 mg on sperm concentration in male participants	Percentage of participants who experience a ≥ 50% decline vs baseline in sperm concentration after Week 24* Percentage of participants reaching the lower limits of normal (LLN) (15 million spermatozoa per mL) in sperm concentration at Week 24*
To evaluate the effect of chronic administration of macitentan 75 mg on reproductive hormones in male participants	Percent changes from baseline to Week 24* in reproductive hormones (follicle stimulating hormone [FSH], luteinizing hormone (LH), testosterone, dihyrotestosterone [DHT], inhibin B, prolactin, estradiol)
To evaluate the reversibility of the effects of macitentan on semen parameters in male participants	Percent change from Week 24* to 12 Weeks after treatment discontinuation in: • semen volume • sperm concentration • sperm motility • sperm morphology
To evaluate the reversibility of the effects of macitentan on sperm concentration in male participants	Percentage of participants who experience a ≥ 50% decline vs Week 24* in sperm concentration 12 weeks after treatment discontinuation Percentage of participants reaching the LLN (15 million spermatozoa per mL) in sperm concentration 12 weeks after treatment discontinuation
To evaluate the reversibility of the effects of macitentan on reproductive hormones in male participants	Percent change from Week 24* to 12 weeks after treatment discontinuation in reproductive hormones
**Analyses to be repeated with week 24 OL data*	

3. STUDY DESIGN

3.1 Overall design

This sub-study will be conducted in selected sites to enroll male participants from UNISUS (AC-055-315) and MACiTEPH (67896062CTP3001) studies. Therefore, visits for the present study are planned to coincide with UNISUS and MACiTEPH study scheduled visits. However, participants who discontinue study treatment will have an extra visit 12 weeks after their treatment discontinuation for blood and semen samples collection (see Section 4).

This is an optional sub-study opened to male participants willing to participate, conducted in selected sites. Male participants who refuse to participate in this sub-study could still participate to the main study. In addition, a participant may withdraw from this sub-study at any time with no impact on his participation to the main study.

This sub-study includes the following periods (see Figure 1):

- **Prior to study intervention exposure**

Male participants enrolled in either UNISUS or MACiTEPH and willing to take part to the testicular function sub-study will sign a separate informed consent form (ICF) at screening and will have their participation recorded in the interactive web response system (IWRS) system.

At baseline, blood and semen samples will be collected prior to the first study intervention dose.

During study intervention exposure

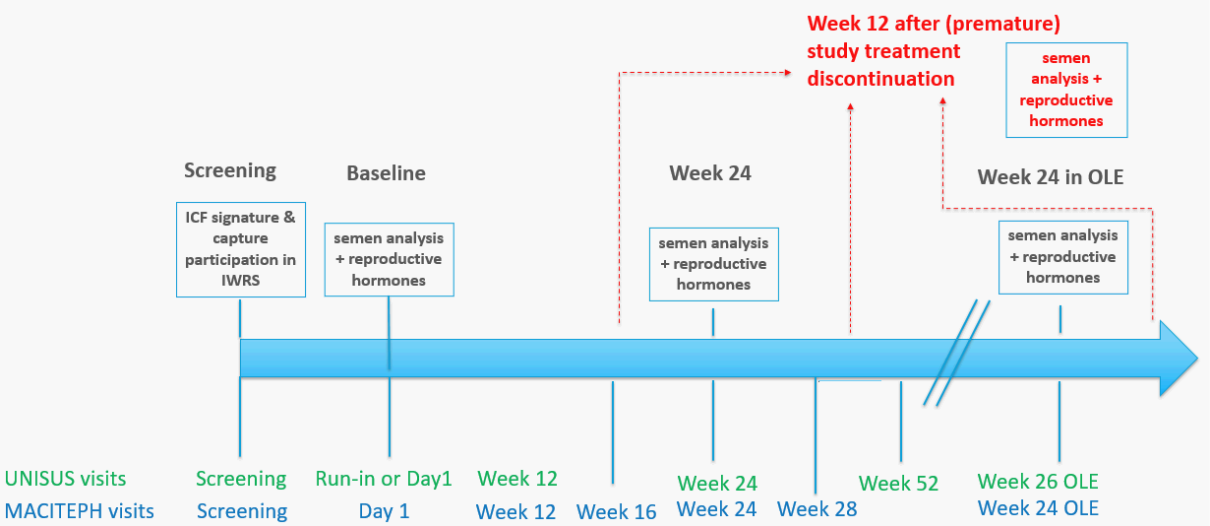
Follow-up samples will be collected at 2 timepoints corresponding to at least one spermatogenesis cycle with macitentan 75 mg treatment:

- Week 24 after initiating study intervention (i.e. macitentan 75 mg or placebo)
- Week 24 after entering into the treatment extension period with an open-label treatment with macitentan 75 mg.

- **After study intervention exposure**

Participants discontinuing their study intervention either prematurely or at the end of the study will have samples collected at approximately 12 weeks after their last dose of study intervention.

Figure 1 Schematic overview of the study



3.2 Scientific rationale

The duration of a spermatogenesis cycle lasts approximately 74 days (ie, 10 weeks) (Heller 1963). The time points of this sub-study have been chosen to assess the effect of macitentan 75 mg on testicular function after exposure for at least one full spermatogenesis cycle. Hence, Week 24 in the double-blind treatment period corresponds to an exposure of 16 and 20 weeks to macitentan 75mg in MACiTEPH and UNISUS, respectively, taking into account their different up-titration scheme.

Since participants will be exposed to either macitentan 10 mg or macitentan 75 mg or placebo during the double-blind treatment period, a second sample will be collected during the open-label treatment extension in order to optimize the number of participants exposed to macitentan 75 mg. The study endpoints will therefore be tested again at this second follow-up timepoint.

The study objectives and endpoints have been defined in line with the guidance provided by the FDA regarding the assessment of testicular function toxicity during drug development (FDA 2018).

4. SCHEDULE OF ACTIVITIES

Period	Screening	Double-blind (DB) treatment period		Open-label (OL) treatment extension period	Post-Treatment Follow-up period
Visit number/name (MACiTEPH)	1	2	12	OL9	Week 12 post-treatment Follow-up
Timing		Day 1	Week 24 (±5d)[d]	OL Week 24 (±5d)[e]	12 weeks after treatment discontinuation (+2 weeks)
Study Procedure					
Informed consent (ICF)[a]	X				
Inclusion/exclusion criteria	X				
Sub-study participation record in IWRS	X				
Semen analyses[b]		X	X	X	X
Reproductive hormones[c]		X	X	X	X

d = days; OL: open-label; ICF: informed consent form; IWRS: interactive web response system.

a. Must be signed before first study-related activity.
b. Semen samples to be collected and analyzed in a specialized local laboratory. Semen analyses (volume, concentration, motility and preparation of smears for morphology) to be conducted within 1-hour of sample collection. Morphology assessment to be conducted after fixing and staining of smears. Restrictions to be observed prior to each semen sample collection: Hot tub/jacuzzi/sauna use within the last 2 weeks, sexual abstinence for at least 2 days, extensive exercise (e.g. biking, horse riding…) for at least 2 days.
c. Blood sample to be collected at the site, preferably in the morning and at the same time of the day for each visit and shipped to the study central laboratory.
d. Participants who prematurely discontinue DB study intervention prior to Week 24 should have a semen- and blood sample collected as soon as possible after the intake of the last dose
e. Participants who prematurely discontinue OL study intervention prior to OL Week 24 should have a semen- and blood sample collected as soon as possible after the intake of the last dose.

5. STUDY POPULATION

5.1 Inclusion criteria

1. Must sign an ICF indicating that he understands the purpose of, and procedures required for, the sub-study and is willing to participate in the sub-study.
2. Male participants enrolled in UNISUS or MACiTEPH studies.
3. Participants ≥18 (or the legal age consent in the jurisdiction in which the study is taking place) and ≤65 (inclusive) years of age.

5.2 Exclusion criteria

1. Participant who has undergone a vasectomy.
2. Treatment with hormone-suppressive agents, including androgens, estrogens, anabolic steroids or glucocorticoids within 6 months prior to baseline or planned during the study.

3. Participants who refuse to abstain from the following prohibited lifestyle choices or activities prior to each semen sample collection:
   a. Hot tub/jacuzzi/sauna use for at least 2 weeks,
   b. Sexual abstinence for at least 2 days,
   c. Extensive exercise (e.g. biking, horse riding…) for at least 2 days.

6. CONCOMITANT THERAPY

The following medications and/or therapies are not allowed to be administered concomitantly with study intervention for participants enrolled in this sub-study:

- Treatment with hormone-suppressive agents, including androgens, estrogens, anabolic steroids or glucocorticoids within 6 months prior to baseline and/or planned to be taken during the study.

7. SUB-STUDY ASSESSMENTS AND PROCEDURES

7.1 Semen parameters

The following non-invasive semen parameters will be assessed in this sub-study and are appropriate surrogate markers for evaluation of testicular toxicity: sperm concentration, semen volume, sperm motility and sperm morphology.

All semen analyses will be performed in accordance with the WHO Guidance (5th edition; WHO Guidance 2010). Instructions for the collection, handling and analyses of semen samples will be provided in the study laboratory manual.

7.2 Blood

A central laboratory will be used for all mandated blood tests. The following blood biomarkers will be assessed in this sub-study and are considered appropriate markers of testicular injury: serum concentrations of total testosterone, DHT, FSH, LH, inhibin B, prolactin, estradiol.

If possible, blood samples for hormones assessment should be conducted preferably in the morning hours due to the diurnal nature of hormones secretion. If this is not possible, the sampling should be done consistently at the same time of the day throughout the sub-study to minimize intra-variability. A total of approximately 11mL of blood will be drawn for the purpose of this sub-study.

Instructions for the collection, handling, storage, and shipment of samples will be described in the laboratory manual.

8. STATISTICAL CONSIDERATIONS

This is a descriptive study to evaluate: the change from baseline at Week 24, i.e. after at least one spermatogenesis cycle with macitentan 75mg in:

- semen parameters
- reproductive hormones,

- percentage of participants who experience a ≥50% decline vs baseline in sperm concentration

In addition, the reversibility of effects on semen and reproductive hormone parameters will be assessed after 12 weeks of discontinuation of macitentan 75 mg treatment.

No statistical hypothesis will be tested. Only descriptive analyses of data will be performed. Thus, the sample size for the study is based on estimating the percent change from baseline in the endpoints after 24 weeks of dosing. Limits of the precision estimates are provided as percentage of the true mean of the percentage of change. The sample size calculation is not based on the proportion of subjects falling within threshold limits. However, these proportions may be estimated from the data during analysis.

8.1 Sample size

The percentage of change from baseline (BL) at post-dose time T is defined as:

Percent change = $100*(X_T- X_{BL})/X_{BL}$

Based on Amory et al. (Amory 2017), an intra-subject coefficient of variation (CV) of 30 and 40% were selected for this sample size determination.

Assuming the sub-study can enroll a sample size ranging between 20 and 50 completers, the lower and upper limits of the precision estimates with a 95% confidence interval, expressed as percentage of the true mean value are given in table 1 when the true percent change is -50%. The corresponding ranges for the percent change are also provided.

Table 1 Percentage change from baseline = -50%

Intra-subject CV (%)	Sample Size - Completers (N)	Precision Estimate Range (as % of true mean) with 95% confidence		Corresponding range for percentage of change with 95% confidence	
		Lower Limit (%)	Upper Limit (%)	Lower Limit (%)	Upper Limit (%)
0.3	20	85	113	-42.5	-56.5
0.3	30	88	110	-44.0	-55.0
0.3	40	90	109	-45.0	-54.5
0.3	50	91	108	-45.5	-54.0
0.4	20	80	116	-40.0	-58.0
0.4	30	85	113	-42.5	-56.5
0.4	40	87	112	-43.5	-56.0
0.4	50	88	110	-44.0	-55.0

Assuming an intra-subject CV of 40% and true percent change (decrease) from baseline equal to -50%, the precision estimates ranges (when expressed as the %of true mean value) will be 80 to 116% for N= 20 completers and 88 to 110% for N= 50 completers, with 95% confidence. Correspondingly, the estimated ranges for the percent change will be -40 to -58% for N= 20 completers and -44 to -55% for N= 50 completers.

8.2 Statistical Methods

The percent change from baseline in semen parameters and reproductive hormones at Week 24, and the reversibility of these parameters will be presented along with 95% confidence intervals. The percentage of participants who experience a ≥50% decline vs baseline in sperm concentration after week 24 will be estimated along with 95% confidence intervals.

8.3 Analyses timepoints

This sub-study will include the following analysis timepoints (AT):

- AT1: once all sub-study participants have reached their week 24 visit during the double-blind treatment period;
- AT2: once all sub-study participants have reached their week 24 visit during the open-label treatment extension period;
- AT3: once all sub-study participants have either completed or prematurely discontinued the sub-study. This analysis timepoint may be skipped if no participant discontinue treatment after AT 2, e.g. all participants continue into a post-trial treatment access program or switch to commercially available treatment with macitentan 75 mg after the end of the study.

10.18 Appendix 18: : Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

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

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

STUDY VISITS

- Missed visits, missed assessments or assessments performed out of window due to COVID-19 will be captured in the clinical trial management system for protocol deviations with the prefix "COVID-19-related", with the actual visit date documented or reason for withdrawal specified. Other relevant study elements impacted by the pandemic should also be documented / labeled as "COVID-19 related" in the clinical trial management system for protocol deviations or other study system, as applicable.
- Discontinuations of study interventions and withdrawal from the study due to COVID-19 will be captured with the prefix "COVID-19-related" in the eCRF.
- Participants entering in screening who are not able to complete all screening and randomization assessments on site due to COVID-19 restrictions (eg, no on-site visit possible) would be considered screening failures. Up to 2 re-screening assessments are permitted in case participant cannot attend randomization visit.
- Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible by remote/virtually/flying nurse service/home visits. This applies to all visits except Visit 1/Screening and Visit 2 (randomization) which must be conducted in person at the study site. Additionally, Visit 3 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 13 (Week 28) and EODBT/OL1, should be done on-site, if possible.

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

  – Involvement of a local registered nurse, or any other properly trained person, site study nurse or the participant's physician to collect required blood samples and/or perform physical examinations, as indicated per protocol (see section 1.2 Schedule of Activities of the Protocol) for planned remote visits.

  – Blood sampling with central laboratory kits may be performed locally and shipped to the central laboratory. Alternatively, a local laboratory may be considered, in case the central laboratory kits cannot be used for the scheduled blood tests.

  – Telephone calls at scheduled visits or monthly at a minimum, if the window for scheduled visits is wider, with participant and their primary care physician, local nurse, etc if applicable.

  – Telemedicine consultation, if permitted by local regulation and if part of the local clinical practice.

  – Review of any available medical records.

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

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

LABORATORY ASSESSMENTS

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

PHARMACOKINETIC, EFFICACY, AND SAFETY ASSESSMENTS

- Enrollment in the hemodynamic sub-studies may be stopped or put on-hold in certain sites or countries if necessary, depending on the status of the pandemic situation or site recommendation.
- The study IDMC will be provided with listings of COVID-19 related protocol deviations and will be asked to evaluate their impact on study safety and efficacy measurements.

TREATMENT

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

HANDLING OF SAFETY AND EFFICACY DATA INTEGRITY

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

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

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

10.19 Appendix 19: Protocol Amendment History

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

Amendment 3 (05-August-2020)

Overall Rationale for the Amendment is:

1. to merge global protocol version 2 and the local VHP version 3 into a new global version to include the changes related to the use of riociguat and the DDI study that were mandated by VHP
2. to implement changes due to an USM (ie, exclusion of patients treated with dual moderate CYP3A4/CYP2C9 inhibitors)
3. to allow the use of SC treprostinil as background PH-specific therapy, since it has received marketing authorization in the EU in April 2020
4. to update the statistical section based on EMA Scientific Advice as well as to make minor updates and corrections and perform editorial document formatting revisions.

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

Section number and Name	Description of Change	Brief Rationale
1.2 Schedule of Activities (SoA): Table 1; 8.2.7 Right Heart Catheterization	Footnote 7 was added: 'Physical examination at Screening will include assessment of the Child Pugh score for participants with known hepatic impairment' Further numbering of the remaining footnotes is changed due to addition of new footnote 7. Footnote 13: 'A historical RHC performed within ~~30~~ **60** days of Randomization can be used as the baseline RHC, provided the criteria for historical RHCs described in the RHC guidelines (Appendix 16) are met.'	Footnote 7: To mandate the proper documentation of hepatic impairment at screening. Footnote 13: To update the extended period for historical RHC which can be used as a baseline RHC for the RHC sub-study.
1.2 Schedule of Activities (SoA): Table 2 Liver Function Tests	Liver function test assessment interval was updated as 'monthly until 52 weeks exposure; every 3-months after 52 weeks exposure'. Also, the corresponding footnote 5 was updated: 'AST/ALT monitoring required **monthly until week 52 if interval between 2 regular site visits exceeds 4 weeks. After 52 weeks exposure in the OL period AST/ALT monitoring required every 3** month~~sly~~ if interval between 2 regular site visits exceeds **12** weeks. Local laboratory can be used.	To update the revised information about liver function test.

Section number and Name	Description of Change	Brief Rationale
2.3.4 Potential Risks	The sentences were revised as: ~~Serious and non serious H~~Hepatic adverse events of special interest (HAESIs) will be reviewed by an International Liver Safety Data Review Board (ILSDRB).	Minor revision to improve the clarity of the matter.
1.1. Synopsis, and 3. Objectives and Endpoints: Exploratory (Double-Blind Treatment Period)	Assessment timepoint specified as 'Week 28' was deleted.	Minor update to incorporate all visit assessments for all exploratory PROs assessed up to 52 weeks.
	Two Impact domains were added for capturing cardiovascular symptom domain score as physical impact score and cognitive/emotional impact score.	To update missing information.
1.1. Synopsis, and 3. Objectives and Endpoints: Safety (Double-Blind Treatment Period)	The sentences were revised as: • All-cause death **up to 30 days after study intervention discontinuation** ~~up to Week 52~~	Minor update to specify all-cause-death period post-treatment discontinuation consistently with other safety parameters.
4.1 Overall Design	The sentences were revised as: In case of premature discontinuation, the DB treatment period ends on the day of intake of the last dose and the EODBT visit is performed within 7 days of ~~taking the decision to stop~~ **intake of the last dose of** study intervention.	To update information about conducting EODBT visit in case of premature discontinuation.
	The reporting of study results is updated as: • The ~~primary~~ final analysis **of the double-blind (DB) study period** will be performed when 144 participants (if there is no sample size increase at interim) have completed the DB period or prematurely discontinued the study. • The final analysis **for the study, including combined DB and OL extension** will be performed after closure of the OL extension period.	To clarify the planned reporting of the study results and remove the potentially misleading text in context to primary analysis.
4.4 End of Study Definition: Table 4	• DB treatment period was specified as **'52-week'** • Footnote 'a' revised as: 'Except withdrawal of consent, **where EOS will be the last visit performed**'	Minor updates to improve the clarity of the matter.
5.1 Inclusion Criteria	Criterion 2 was revised as: 'Male or female ≥18 **(or the legal age of consent in the jurisdiction in which the study is taking place)** and ≤80 years of age.'	To specify the age range accepted in particular jurisdiction.

Section number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	A footnote was added for criterion 16 related to hepatic impairment as follows: 'The assessment for hepatic impairment must be fully documented in the medical history for participants that have clinical signs and evidence (from central and local labs) of hepatic impairments at screening'	To mandate the proper documentation of hepatic impairment at screening.
5.1 Inclusion criteria	Participants are to receive riociguat as per local standard of care, unless riociguat is contraindicated or unavailable	To ensure that all participants, for whom standard of care with riociguat is appropriate, receive riociguat (update previously captured in Version 3.VHP)
6.5 Concomitant therapy	Clarification added that participants should receive riociguat as per local standard of care, unless riociguat is contraindicated or unavailable. The reasons for a participant not receiving riociguat must be documented.	To ensure that all participants, for whom standard of care with riociguat is appropriate, receive riociguat and that the reasons for riociguat treatment being considered inappropriate are documented (update previously captured in Version 3.VHP).
6.5 Concomitant therapy	Changes in exposure which would necessitate a dose adaptation of riociguat were pre-specified.	Criteria for a potential clinically significant DDI between macitentan 75 mg and riociguat have been pre-defined to allow co-administration of riociguat as soon as the DDI results are available, and without the need for a substantial amendment (update previously captured in Version 3.VHP).
6.5.1. Rescue Medication	The sentences were revised as: PDE-5 inhibitors, prostacyclin, prostacyclin analogs, prostacyclin receptor agonist **(Their administration will not require study intervention discontinuation and participants can remain in the study)**.	Wordings added for clarification
7.1.2 Temporary Discontinuation	Study interruption/treatment discontinuation period after which treatment to be reinitiated was corrected. The sentences were revised as: Longer interruptions **(ie>5 consecutive days during each DB up-titration step, >14 consecutive days during the DB maintenance- and OL period, or > 28 days in total)** must lead to **permanent** study intervention discontinuation.	To rectify the error; to state that longer interruptions will lead to permanent study discontinuation.

Section number and Name	Description of Change	Brief Rationale
8.1 Demographics and Baseline Characteristics	The sentences were revised as: Demographic and baseline characteristic data to be collected on all randomized participants include: age, sex, race and ethnicity (where local regulations permit), date of the initial CTEPH diagnosis, 6MWD, WHO FC, **date of most recent CTEPH hospitalization, number of previous hospitalizations for CTEPH within 6 months prior to Screening, Child Pugh Score for participants with known hepatic impairment**.	To describe additional baseline data to be captured for all randomized participants.
8.2.1 6-minute walk test	The sentence was updated as: **If the participant wears a mask during the 6MWT, this will be documented in the eCRF**	To state that this information should be captured during the conduct of 6-MWT during COVID-19
8.2.5 Accelerometry	The sentences were revised as: The vendor ~~will read daily counts/minute and~~ will ~~analyze~~ **derive activity counts and will provide** ~~duration of~~ daytime activity and time (minutes) spent in sedentary, light, moderate and vigorous physical activity **based on these activity counts**.	To specify the exact procedure for vendor to capture the accelerometry assessment data.
8.2.7 Right Heart Catheterization	The sentences were revised as: For participants who underwent PEA or BPA, the time between the procedure and the RHC must be at least 24 ~~and 12~~ weeks~~, respectively~~. **PH-specific therapy must be stable for at least 90 days prior to the baseline RHC.**	To correct error and align with inclusion criteria To indicate PH-specific therapy stability requirement prior to baseline RHC in the RHC sub-study.
8.3.5 Clinical Safety Laboratory Assessments	The sentences were revised as: For monthly **(3-monthly after 52 weeks exposure in the OL period)** AST/ALT monitoring in between visits, a local laboratory can be used. If the local laboratory results show an increase in AST/ALT ≥3x ULN, the participant must return to the site and the AST/ALT re-test must be performed centrally. **Only abnormal local laboratory results must be recorded in the eCRF.**	To specify additional safety related information to be captured from local laboratory AST/ALT assessments.
8.3.5 Clinical Safety Pregnancy tests	The sentence was revised as: For women of childbearing potential, a serum pregnancy test will be performed ~~at each regular site visit~~ **at the**	To update information about frequency and timepoints to conduct serum pregnancy test.

Section number and Name	Description of Change	Brief Rationale
	frequency defined in the schedule of activities.	
8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The requirement for reporting SAEs was updated: *[…] within 24 hours of their knowledge of the event* was replaced by *[…] immediately, without undue delay, and under no circumstances later than 24 hours following knowledge of the event.*	To address the comment that the protocol wording was not aligned with the detailed 2011/C 172/01 (EU) CT-3 guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (update previously captured in Version 3.VHP).
8.4.3. Regulatory Reporting Requirements for Serious Adverse Events	Text removed from protocol: The SAEs listed below that are expected to occur in participants with PAH will be considered as 'disease-related' and 'expected' for regulatory reporting purposes in this population, unless fatal or life-threatening. Signs and symptoms of PH worsening/exacerbation/progression and, in particular, abdominal pain, anorexia, chest pain, cyanosis, diaphoresis, dizziness, pre-syncope, dyspnea, orthopnea, fatigue, hemoptysis, heart failure, hypoxia, palpitations, syncope, collapse, systemic arterial hypotension, and tachycardia. The investigator must report these in the AE section of the eCRF and on an SAE form. For expedited reporting purposes, these SAEs will be treated as 'disease-related' and expected and will therefore not require systematic unblinding and will not require expedited reporting to Health Authorities, IECs/IRBs, and investigators.	Due to Actelion integration in Janssen Pharmaceutical and in application to its operating procedures, these serious adverse events will be reported as any other SAE.
8.4.4. Pregnancy	The sentences were revised as: All initial reports of pregnancy in female participants **or partners of male participants** must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal	To capture reproduction-related information in case of all study participants and to comply with internal procedures. Cross-reference to Section 7 corrected to relevant subsection.

Section number and Name	Description of Change	Brief Rationale
	pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. For more information on the action that should be taken towards study intervention in case a participant becomes pregnant during the study, please refer to Section ~~7.1.2.~~ **7.1.1.**	
8.4.5 Adverse Events of Special Interest	Information in Liver event updated to specify a particular SAE. **All events of ALT (or AST) ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event.**	To update information about SAE reporting in case of elevated ALT, AST and total bilirubin levels, indicating sever liver injury.
8.7 Pharmacodynamics	The sentence was revised as: **Sparse sampling consists of a pre dose and a 2-10 hours post-dose ET-1 sample.**	To state additional information about sparse sampling.
9.3 Population of Analyses	Following points related to analysis set were revised as: 2. **Final analysis of DB study period** when all participants have completed Week 52 or prematurely discontinued the study, 3. Final analysis **of study**: when all participants have completed the OL extension period. Safety analysis set (SAS): Participants will be analyzed according to the intervention they actually received ~~at randomization~~ (which may be different to the study intervention arm they are assigned to via IRS)	To clarify the planned reporting of the study results and remove the potentially misleading text in context to primary analysis.
Synopsis; 9.4.1. Primary Efficacy Analysis: Estimand-C: Intercurrent events	The sentences were revised as: All scheduled assessments following the date of death will be replaced by a 'worst-case' imputation, ie, the lowest observed value of 6MWD change from baseline across both treatment groups and over all assessments **up to Week 28.**	To clarify the assessments used in imputation

Section number and Name	Description of Change	Brief Rationale
	The sentences were revised as: All 6MWD assessment performed **after end of intervention (possibly treatment related) plus 7 days or after administration of rescue therapy** ~~these intercurrent events~~ will be ignored in the analysis and for each visit occurring after the IE, the minimum of the following values: (1) the last observed value **(observed 6MWD change from baseline)** prior to intercurrent event at the participant level and (2) the 25th percentile of observed 6MWD change from baseline values (both treatment groups pooled and over all assessments **up to Week 28**), will be considered instead.	To correct the error in the intercurrent event with respect to end of intervention adding plus 7 days
9.4.1. Primary Efficacy Analysis: Handling of missing data	The sentences were updated as: **The imputation of change from baseline will be bound by the baseline value so that any worsening cannot be greater than baseline value and no improvement from baseline will be imputed for missing or replacement of assessments following these intercurrent events.**	To prevent impossible values or implausible improvement following imputation of intercurrent events.
9.4.1. Primary Efficacy Analysis: Main analysis	The sentences were revised as: **Type I error control with respect to conducting an unblinded sample size re-estimation will be detailed in the SAP.**	To clarify that a two-stage testing procedure will be detailed in the SAP
9.4.1. Primary Efficacy Analysis: Sensitivity analyses	The sentences were revised as: • **An analysis will be conducted to assess the robustness of the results of the main analysis handling deaths before / after rescue therapy in the same way so that if a participant dies while on rescue therapy the imputation rules for death will be applied.**	To assess robustness of handling deaths before / after rescue therapy
9.4.1. Primary Efficacy Analysis: Supplementary Analyses; Table 13 Supplementary Estimands of the Primary Endpoint	Contents of the table modified as per study needs. Supplementary Estimand 1: clarification of handling missing **Treatment policy – as not IE, values after end of intervention plus 7 days are included**	Supplementary estimand 1- Similar clarification were done to the intercurrent events as per the primary endpoint estimand. Text added to clarify handling of missing data under MMRM. Clarification added to type of data used and imputations in supplementary estimand 2a IE (possibly treatment related) and to

Section number and Name	Description of Change	Brief Rationale
	Supplementary Estimand 2a: Last observation carried forward **in case of missing data, values after EOT are included** LOCF for **missing values** **Treatment policy – values after end of intervention are included** Supplementary Estimand 2b was updated as: • Supplementary Estimand 2b aims to provide results using MMRM as in the primary estimand while implementing a treatment policy strategy with respect to treatment discontinuations and rescue medication with a reference-based multiple imputation method for missing data. Non-parametric (Gould-type) approach will also be considered using time-to death for participants who die being ranked below all surviving participants. Whole column under Supplementary Estimand 2b is added.	indicate that missing data will be handled based on the treatment policy strategy Supplementary Estimand 2b is newly added to first provide results using MMRM as in the primary estimand while implementing a treatment policy strategy with respect to treatment discontinuations and rescue medication with a reference-based multiple imputation method for missing data. In addition, a non-parametric (Gould-type) approach will also be considered using time-to death for participants who die being ranked below all surviving participants.

Section number and Name	Description of Change	Brief Rationale
9.4.2.1 Time to first clinical worsening up to Week 52	Previous information about population-based analyses, exploratory analyses and sensitivity analyses was updated. The sentences were revised as: The first secondary efficacy endpoint is time to **CEC-confirmed** clinical worsening up to Week 52 (see definition in Section 3). **The number of participants with a CEC-confirmed clinical worsening by first event type (eg, all-cause death) will be presented.** **Exploratory analyses will be conducted for time to first CEC-confirmed event for each event type separately. Participants who do not have a CEC-confirmed clinical worsening event type will have their time to clinical worsening right-censored at earliest among the following times:** • **CEC-confirmed clinical worsening event (any other event type)** • **Study intervention discontinuation + 7 days.** • **Week 52.** **Sensitivity analyses will be conducted for time to first CEC-confirmed clinical worsening using a modified definition of clinical worsening to exclude the following:** **1. Initiation or dose escalation of PH-specific therapy due to worsening of PH based on additional assessments performed at the discretion of the investigator and confirmed by the CEC** **2. In addition, exploratory analyses will be conducted for time to first "suspected clinical worsening" with same definition as for the secondary endpoint but based on investigator judgment.**	Addition of sensitivity and exploratory analyses for the first secondary endpoint
9.4.2.2 Improvement in WHO FC from baseline to last value while on	The sentences were revised as: Assessments that are after **(possibly treatment related)** discontinuation of study intervention +7 days and/or	To clarify handling of intercurrent events and missing data due to other reasons

Section number and Name	Description of Change	Brief Rationale
treatment up to Week 28 (yes/no)	administration of rescue CTEPH therapy are excluded from the analysis. The 75th percentile (from ~~lowest~~ observed WHO FC change from baseline across both treatment groups and over all assessments) will be imputed to Week 28 following these intercurrent events. Missing values at Week 28 **(for reasons other than described above)** will be imputed by carrying forward the last assessment before discontinuation of study intervention +7 days and/or administration of rescue CTEPH therapy.	
9.4.2.3 Change from baseline to last value while on treatment up to Week 28 in PAH-SYMPACT®: Analysis	The sentences were revised as: Assessments that are after **possible treatment related** discontinuation of study intervention +7 days and/or administration of rescue CTEPH therapy are excluded from the analysis. The **maximum**~~inimum~~ of the following values: (1) the last observed value **(change from baseline)** prior to intercurrent event at the participant level and (2) the 7~~2~~5th percentile of observed change from baseline values (both treatment groups pooled and over all assessments) will be imputed to Week 28 following these intercurrent events.	To clarify handling of intercurrent events and missing data due to other reasons
9.4.2.5 Change from baseline to Week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity	The sentences were revised to update minor clarification. • Assessments that are after **(possibly treatment related)** discontinuation of study intervention +7 days and/or administration of rescue CTEPH therapy are excluded from the analysis. The minimum of the following values: (1) the last observed value **(change form baseline)** prior to intercurrent event at the participant level and (2) the 25th percentile of observed change from baseline values (both treatment groups pooled and over all assessments) will be imputed to Week 28 following these intercurrent events.	To clarify handling of intercurrent events and missing data due to other reasons

Section number and Name	Description of Change	Brief Rationale
Synopsis; 9.4.3 Safety Analyses:	Pulmonary Function Tests was deleted: ~~Pulmonary Function Tests~~ ~~Descriptive statistics of PFTs (FEV1 and FVC) values and changes from baseline will be summarized by intervention group.~~	PFT data not to be collected post baseline.
Table 8 footnote	Footnote related to RHC was updated stating that the **submission of RHC tracing is optional**.	To clarify that the RHC tracing submission is optional.
Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Removal of reference to disease-related SAEs in Section 8.4.4.	Due to Actelion integration in Janssen Pharmaceutical and in application to its operating procedures, these serious adverse events will be reported as any other SAE.
Appendix 14: Patient Health Questionnaire (PHQ-8)	A revised PHQ-8 questionnaire is included.	To correct formatting of the PHQ-8.
Appendix 16: Actelion Heart catheterization guidance	Following statement was deleted at all instances in Appendix 16:'Values must be recorded as they were consecutively measured.'	To align with Actelion Heart Catheterization guidelines
Appendix 17: COVID-19 Appendix	Study-specific COVID-19 appendix is included.	New appendix added to provide guidance during the COVID-19 pandemic.
Throughout the protocol	• The term 'Subcutaneous OR SC' in connection with prostanoids was deleted to indicate that the participants with background PH-specific therapy with SC prostacycins can be benefitted from current study intervention. • Minor grammatical, formatting and spelling changes were made.	Updates were made to correct minor errors noted during the authoring of this amendment.

Amendment 2 (13 July 2020)

Overall Rationale for the Amendment: The purpose of this amendment was to update the exclusion criteria and concomitant therapy sections pertaining to new information regarding a drug-drug-interaction of macitentan 75 mg with moderate dual CYP3A4 and CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors.

A Protocol Amendment Summary of Changes Table for the current amendment is provided below.

Section number and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria - Exclusion criteria related to macitentan use	The exclusion criterion 21 was updated. 1. Treatment with strong CYP3A4 inhibitors~~,~~ **(**eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir**) or moderate dual CYP3A4/CYP2C9 inhibitors (eg, fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (eg, miconazole, piperine)**, within 30 days prior to Randomization.	To exclude participants who, within 30 days of Randomization, received treatment with a moderate dual CYP3A4/CYP2C9 inhibitor or who received a combination of moderate CYP3A4- and moderate CYP2C9 inhibitors.
2.2 Background (Clinical Studies - Human Pharmacokinetics)	New information on concomitant administration of CYP34A and CYP2C9 inhibitors was added as follows. 2. Concomitant use of macitentan with strong inhibitors or inducers of CYP3A4 **or moderate dual CYP3A4/CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors** should be avoided.	To add moderate dual CYP3A4/CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4- and moderate CYP2C9 inhibitors to the list of forbidden medications.
6.5 Concomitant therapy	New information on concomitant administration of CYP34A and CYP2C9 inhibitors was added. 3. Strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir) **or moderate dual CYP3A4/CYP2C9 inhibitors (eg, fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 (eg, ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitors (eg, miconazole, piperine).**	
6.5 Concomitant Medication; 11 References	A new reference was added to Section 6.5 and to the reference list.	To provide investigators with some examples of CYP3A4 and CYP2C9 inhibitors

Amendment 1 (22 April 2020)

Overall Rationale for the Amendment: The protocol was amended to ensure that all participants, for whom standard of care with riociguat is appropriate, receive riociguat in the study. Furthermore, information on the ongoing drug-drug interaction (DDI) study with riociguat is provided, and the criteria for concomitant riociguat therapy (in the absence of a clinically relevant DDI) to be permitted without the need for a substantial amendment are defined.

Section number and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	Participants are to receive riociguat as per local standard of care, unless riociguat is contraindicated or unavailable	To ensure that all participants, for whom standard of care with riociguat is appropriate, receive riociguat
6.5 Concomitant therapy	Clarification added that participants should receive riociguat as per local standard of care, unless riociguat is contraindicated or unavailable. The reasons for a participant not receiving riociguat must be documented.	To ensure that all participants, for whom standard of care with riociguat is appropriate, receive riociguat and that the reasons for riociguat treatment being considered inappropriate are documented.
2.2 Background	The ongoing DDI study with riociguat is described in the 'clinical studies' section.	To provide information on the ongoing DDI study with riociguat.
6.5 Concomitant therapy	Changes in exposure which would necessitate a dose adaptation of riociguat were pre-specified.	Criteria for a potential clinically significant DDI between macitentan 75 mg and riociguat have been pre-defined to allow co-administration of riociguat as soon as the DDI results are available, and without the need for a substantial amendment.
8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The requirement for reporting SAEs was updated: *[…] within 24 hours of their knowledge of the event* was replaced by *[…] immediately, without undue delay, and under no circumstances later than 24 hours following knowledge of the event.*	To address the comment that the protocol wording was not aligned with the detailed 2011/C 172/01 (EU) CT-3 guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use.

11 REFERENCES

(D-16.563) A Phase 1/1b, open-label study in patients with recurrent glioblastoma to assess the safety and tolerability of macitentan in combination with dose-dense temozolomide. Actelion Pharmaceuticals Ltd; Clinical Study Report, AC-055-115, 4 January 2017.

(D-17.238) A single-center, open-label, Phase 1 study of macitentan, radiotherapy and temozolomide concurrent therapy followed by maintenance therapy with macitentan and temozolomide in subjects with newly diagnosed glioblastoma. Actelion Pharmaceuticals Ltd; Clinical Study Report, AC-055-118, 17 August 2017.

(ATS Statement 2002) ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002;166:111-117.

(Albassam 2001) Albassam MA, Metz AL, Potoczak RE, et al. Studies on coronary arteriopathy in dogs following administration of CI-1020, an endothelin A receptor antagonist. Toxicol Pathol. 2001;29:277-284.

(Amory 2017) Amory JK, Wang C, Swerdloff RS, et al. The effect of 5alpha-reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab. 2007;92(5):1659-1665

(Bauer 2002) Bauer M, et al. Selective Upregulation of Endothelin B Receptor Gene Expression in Severe Pulmonary Hypertension, Circulation. 2002;105(9):1034-1036.

(Boucly 2017) Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017;50(2).

(Borg 1982) Borg G. Psychophysical basis of perceived exertion. Medicine and Science in Sports and exercise. 1982; 14 (5), 377-381.

(Borg 1998) Borg G. Borg's perceived exertion and pain scales. Human Kinetics. ISBN: 0-88011-623-4.

(Chin 2018) Chin KM, Gomberg-Maitland M, Channick RN, et al. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results of the SYMPHONY Trial. Chest. 2018;154(4):848-861. doi: 10.1016/j.chest.2018.04.027. Epub 2018 Apr 26.

(Clozel 2006) Clozel M, Flores S. Endothelin receptors as drug targets in chronic cardiovascular diseases: the rationale for dual antagonism. Drug Develop Res 2007;67:825-834.

(Dogterom 1992) Dogterom P, Zbinden G, Reznik GK. Cardiotoxicity of vasodilators and positive inotropic/vasodilating drugs in dogs: an overview. Crit Rev Toxicol. 1992;22:203-241.

(FDA 2018) Guidance document on: testicular toxicity: evaluation during drug development. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testicular-toxicity-evaluation-during-drug-development. Accessed 11 December 2020.

(FDA 2020) Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (Table 2-2). https://www fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 09 July 2020.

(Galie 2005) Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension.N Engl J Med. 2005;353(20):2148-2157.

(Galie 2008) Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008;117(23):3010-3019.

(Galiè 2016) Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.

(Ghofrani 2013a) Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension, N Engl J Med 2013;369:319-329.

(Ghofrani 2013b) Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the Treatment of Pulmonary Arterial Hypertension N Engl J Med 2013; 369:330-340.

(Ghofrani 2017) Ghofrani HA, Simonneau G, D'Armini AM, et al; MERIT study investigators. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med. 2017;5(10):785-794. doi: 10.1016/S2213-2600(17)30305-3. Epub 2017 Sep 11.

(Girgis 2005) Girgis RE, Champion HC, Diette GB, Johns RA, Permutt S, Sylvester JT. Decreased exhaled nitric oxide in pulmonary arterial hypertension: response to bosentan therapy. Am J Respir Crit Care Med 2005;172:352-357.

(Gopalan 2016) Gopalan D, Blanchard D, Auger WR. Diagnostic Evaluation of Chronic Thromboembolic Pulmonary Hypertension. Ann Am Thorac Soc. 2016;13 Suppl 3:S222-239.

(Heller 1963) Heller CG, Clermont Y. Spermatogenesis in man: an estimate of its duration. Science. 1963;140(3563):184-186.

(Hettmansperger 2011) Hettmansperger TP, McKean JW, Robust Nonparametric Statistical Methods, Second Edition, 2011.

(Hoeper 2017) Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50(2).

(Humbert 2010) Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension pathophysiology Eur Respir Rev. 2010;19(115):59-63.

(Iglarz 2008) Iglarz M, Binkert C, Morrison K, et al. Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist. J Pharmacol Exp Ther. 2008;327:736-745.

(Iglarz 2010) Iglarz M, Clozel M. At the heart of tissue: endothelin system and end-organ damage. Clin Sci (Lond). 2010;119(11):453-463.

(Iglarz 2014) Iglarz M, Loriette-Steiner P, Pasquali A, Clozel M. Vascular ETB receptors do not mediate relaxation but induce vasoconstriction in experimental pulmonary hypertension (abstract). Am J Respir Crit Care Med. 2014;189:A3344.

(Iglarz 2015) Iglarz M, Landskroner K, Bauer Y, et al. Comparison of Macitentan and Bosentan on Right Ventricular Remodeling in a Rat Model of Non-vasoreactive Pulmonary Hypertension. J Cardiovasc Pharmacol. 2015;66(5):457-467.

(Janssen 2013) Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-1727.

(Jasmin 2001) Jasmin JF, Lucas M, Cernacek P, Dupuis J. Effectiveness of a nonselective ET(A/B) and a selective ET(A) antagonist in rats with monocrotaline-induced pulmonary hypertension. Circulation 2001;103(2):314–318.

(Jenkins 2013) Jenkins DP, Madani M, Mayer E, et al. Surgical treatment of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2013;41(3):735-742.

(Kakoki 1999) Kakoki M, Hirata Y, Hayakawa H, et al. Effects of hypertension, diabetes mellitus, and hypercholesterolemia on endothelin type B receptor-mediated nitric oxide release from rat kidney. Circulation 1999;99:1242-1248.

(Suda 2012) Suda R, Tanabe N, Kato F, et al. Diffusing capacity for carbon monoxide and mortality in patients with chronic thromboembolic pulmonary hypertension. European Respiratory Journal 2012;40(Suppl 56).

(Kato 2014) Kato F, Tanabe N, Urushibara T, et al. Association of Plasma Fibrinogen and Plasminogen With Prognosis of Inoperable Chronic Thromboembolic Pulmonary Hypertension. Circ J. 2014;78(7):1754-1761.

(Kim 2019) Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53:1801915.

(Kroenke 2001) Kroenke K, Spitzer RL, Williams JBW. The PHQ-8. Validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606-613.

(Kunita-Takanezawa 2014) Kunita-Takanezawa M, Abe K, Hirooka Y, et al. Novel Dual Endothelin Receptor Antagonist Macitentan Reverses Severe Pulmonary Arterial Hypertension in Rats. J Cardiovasc Pharmacol. 2014; 64:473-480.

(Lang 2013) Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J. 2013;41: 462-468.

(Lang 2016) Lang IM, Dorfmüller P, Vonk Noordegraaf A. The pathobiology of chronic thromboembolic pulmonary hypertension. Ann Am Thorac Soc. 2016;13:Suppl. 3:S215–S221.

(Lehmacher 1999) Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 1999;55:1286–1290.

(Louden 2001) Louden C, Morgan DG. Pathology and pathophysiology of drug-induced arterial injury in laboratory animals and its implications on the evaluation of novel chemical entities for human clinical trials. Pharmacol Toxicol. 2001;89:158-170.

(Macitentan IB) Investigator's Brochure: JNJ-67896062 OPSUMIT® (Macitentan), Version 17. Actelion Pharmaceuticals Ltd. (January 2020).

(Maruish 2011) Maruish ME (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: Quality Metric Incorporated; 2011.

(Mayer 2011) Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry J Thorac Cardiovasc Surg 2011; 141(3):702-710.

(Mcduffie 2006) Mcduffie JE, Yu X, Sobocinski G, Song Y, Chupka J, Albassam M. Acute coronary artery injury in dogs following administration of CI-1034, an endothelin A receptor antagonist. Cardiovasc Toxicol. 2006;6:25-38.

(Miyamoto 2000) Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000;161(2 Pt 1):487-492.

(Nadeau 2017) Nadeau V, Potus F, Boucherat O, et al. Dual ETA/ETB blockade with macitentan improves both vascular remodeling and angiogenesis in pulmonary arterial hypertension. Pulmonary Circulation. 2017;8(1):1-15.

(NICE 2018) Position statement on use of the EQ-5D-5L valuation set for England (updated November 2018). Accessed on 30 April 2019. Available at: https://www nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l

(Provencher 2006) Provencher S, Sitbon O, Humbert M, et al. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J. 2006;27(5):589-595.

(Pulido 2013) Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369:809-818.

(Ramos 2016) Ramos RP, Ferreira EVM, Fonseca AXC, et al. Prognostic role of excessive exercise ventilation in non-operable patients with chronic thromboembolic pulmonary hypertension. European Respiratory Journal 2016; 48(suppl 60).

(Reilly 1993) Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a Work Productivity and Activity Impairment Instrument. Pharmaco Economics 1993;4(5):353-365.

(Richter 2017) Richter MJ, et al. The prognostic relevance of oxygen uptake in inoperable chronic thromboembolic pulmonary hypertension. Clinical Respiratory Journal 2017;11(6):682-690.

(Rubin 2002) Rubin, LJ, Badesch DB, Barst RJ, et al. Bosentan Therapy for Pulmonary Arterial Hypertension. N Engl J Med 2002; 346:896-903

(Simonneau 2017) Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26:160112 [https://doi.org/10.1183/16000617.0112-2016].

(Simonneau 2019) Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913.

(Sitbon 2019) Sitbon O, Gomberg-Maitland M, Granton J, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. Eur Respir J. 2019; 53[https://doi.org/10.1183/13993003.01908-2018].

(Tsiatis 1987) Tsiatis AA, Rosner GL, Mehta CR. Exact confidence intervals following a group sequential test. Biometrics 1987; 40:797–803

(Van Hout 2012) Van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-715.

(WHO Guidance 2010) WHO laboratory manual for the examination and processing of human semen, Fifth edition, 31 January 2010. https://www.who.int/publications/i/item/9789241547789. Accessed 11 December 2020.

(WHO Report) Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives, WHO Technical report series. (accessed on 16-July-2019). Available at: http://www.who.int/bloodproducts/publications/WHO_TRS_840_A2.pdf.

INVESTIGATOR AGREEMENT

JNJ-67896062 / ACT-064992 macitentan Clinical Protocol 67896062CTP3001 (Amendment 4)

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutica NV

Signature: PPD Date: 16 DEC 2020

(Day Month Year)

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

Confidential – FOIA Exemptions Apply in U.S. 185

Status: Approved, Date: 16 December 2020

Actelion Pharmaceuticals Ltd
Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A prospective, randomized, double-blind, multicenter, placebo-controlled, parallel group, adaptive Phase 3 study with open-label extension to evaluate efficacy and safety of macitentan 75 mg in inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension.

MACiTEPH

Macitentan in inoperAble or persistent/reCurrent chronIc ThromboEmbolic Pulmonary Hypertension

Protocol 67896062CTP3001; Phase 3

JNJ-67896062 / ACT-064992 (macitentan)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Actelion Pharmaceuticals Ltd; Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

IND: 77258

EudraCT NUMBER: 2019-004131-24

Status:	Final
Date:	3 August 2020
Prepared by:	Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document number:	D-20.277

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

Confidentiality Statement

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

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

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

STUDY VISITS

- Missed visits, missed assessments or assessments performed out of window due to COVID-19 will be captured in the clinical trial management system for protocol deviations with the prefix "COVID-19-related", with the actual visit date documented or reason for withdrawal specified. Other relevant study elements impacted by the pandemic should also be documented / labeled as "COVID-19 related" in the clinical trial management system for protocol deviations or other study system, as applicable.
- Discontinuations of study interventions and withdrawal from the study due to COVID-19 will be captured with the prefix "COVID-19-related" in the eCRF.
- Participants entering in screening who are not able to complete all screening and randomization assessments on site due to COVID-19 restrictions (eg, no on-site visit possible) would be considered screening failures. Up to 2 re-screening assessments are permitted in case participant cannot attend randomization visit.
- Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible by remote/virtually/flying nurse service/home visits. This applies to all visits except Visit 1/Screening and Visit 2 (randomization) which must be conducted in person at the study site. Additionally, Visit 3 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 13 (Week 28) and Visit 15 (EODBT/OL1/Week 52), should be done on-site, if possible.

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

  - Involvement of a local registered nurse, or any other properly trained person, site study nurse or the participant's physician to collect required blood samples and/or perform physical examinations, as indicated per protocol (see section 1.2 Schedule of Activities of the Protocol) for planned remote visits.
  - Blood sampling with central laboratory kits may be performed locally and shipped to the central laboratory. Alternatively, a local laboratory may be considered, in case the central laboratory kits cannot be used for the scheduled blood tests.
  - Telephone calls at scheduled visits or monthly at a minimum, if the window for scheduled visits is wider, with participant and their primary care physician, local nurse, etc if applicable.
  - Telemedicine consultation, if permitted by local regulation and if part of the local clinical practice.
  - Review of any available medical records.

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

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

LABORATORY ASSESSMENTS

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

PHARMACOKINETIC, EFFICACY, AND SAFETY ASSESSMENTS

- Enrollment in the hemodynamic sub-studies may be stopped or put on-hold in certain sites or countries if necessary, depending on the status of the pandemic situation or site recommendation.
- The study IDMC will be provided with listings of COVID-19 related protocol deviations and will be asked to evaluate their impact on study safety and efficacy measurements.

TREATMENT

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

HANDLING OF SAFETY AND EFFICACY DATA INTEGRITY

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

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

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

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd and Janssen Research & Development, a division of Janssen Pharmaceutica NV

PPD

Signature: _____ Date: 03AUG2020
(Day Month Year)

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