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

Macitentan / Tadalafil

Pulmonary Arterial Hypertension

Protocol AC-077A301

A DUE

Prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy

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SPONSOR CONTACT DETAILS

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Medical Emergency Hotline Toll phone number:	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6, Version 7	21 November 2022
Amendment 5, Version 6	27 April 2021
Amendment 4, Version 5	20 October 2020
Amendment 3, Version 4	17 July 2020
Amendment 2, Version 3	28 February 2020
Amendment 1, Version 2	12 August 2019
Original Protocol, Version 1	22 February 2019

Amendment 6 Version 7 (21 November 2022)

Overall Rationale for the Amendment: To capture participant experience while on M/T FDC, a semi- structured qualitative interview substudy will assess the participant's experience with study treatment, with regard to satisfaction with treatment regimen and adherence to treatment.

The Changes made to the clinical protocol AC-077A301 as part of Protocol Amendment 6 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 14.11 Appendix 11: Protocol Amendment History.

Section Number and Name	**Description of Change**	**Brief Rationale**
Protocol Synopsis	Updated as per changes made to the protocol body text	To obtain information on patient's experience with FDC
7.1.2 Unscheduled visits	Table 5 Open label treatment period visit and assessment schedule is updated to add the qualitative interview and footnote 13 is added	To obtain information on patient's experience with FDC
7.2.2.12 Qualitative Interview	A new subsection on Semi structured qualitative interview, including its description and design is added	To capture participant experience while on M/T FDC, a semi structured qualitative interview substudy will assess the patient's experience with study treatment, satisfaction with treatment regimen, and adherence to treatment.
9.1.2 Intensity of adverse events	Updated AE reporting process if there is a change in intensity as per Janssen SAE/AE reporting process	To fulfill the HA requirement
3.1 Study Design, 10.4 Interim Analysis for Efficacy, Futility, and Adaptive Sample Size Re estimation	Text is rephrased to clarify that the IA will only include data from countries in which the global amendment 5 has been approved	This clarification was made via a Protocol Clarification Communication issued on 10 Sep 2021 (prior to IA conducted in March 2022)
Throughout the protocol	Minor grammatical, formatting, or spelling changes are made.	Minor errors were noted

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWT	6-minute walk test
6MWD	6-minute walk distance
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BMI	Body mass index
BSA	Body surface area
CEC	Clinical Event Committee
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CL	Confidence limit
CO	Cardiac output
CRO	Contract Research Organization
CSR	Clinical Study Report
CSS	Combination safety set
CTT	Clinical Trial Team
CYP	Cytochrome P450
DBP	Diastolic blood pressure
dPAP	Diastolic pulmonary artery pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDBT	End of Double-blind Treatment
eGFR	Estimated glomerular filtration rate
EOLT	End of Open-Label Treatment
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	Euro Quality of Life-5D-5L
ERA	Endothelin receptor antagonist
FAS	Full Analysis Set
FC	Functional class
FDC	Fixed dose combination
FEV_1	Forced expiratory volume in 1 second

FVC	Forced vital capacity
GCP	Good Clinical Practice
GM	Geometric mean
GMP	Good Manufacturing Practice
GMR	Geometric means ratio
HIV	Human immunodeficiency virus
HR	Heart rate
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LHC	Left heart catheterization
LFT	Liver function tests
LS	Least squares
LTFDCS	Long-term M/T FDC Set
LVEDP	Left ventricular end-diastolic pressure
M/M	Morbidity/Mortality
M/T	Macitentan/tadalafil
mCTMS	Medidata clinical trial management system
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end-stage liver disease
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
NT-proBNP	N-terminal pro B-type natriuretic peptide
OLS	Open-label Set
OR	Odds ratio
PA	Pulmonary artery
PAC	Pulmonary artery compliance
PAH	Pulmonary arterial hypertension

PAP	Pulmonary arterial pressure
PAPi	Pulmonary artery pulsatility index
PAWP	Pulmonary artery wedge pressure
PDE-5	Phosphodiesterase type-5
PDE-5i	Phosphodiesterase type-5 inhibitor
PGA-S	Patient Global Assessment of Severity
PGI-C	Patient Global Impression of Change
PI	Principal Investigator
PQC	Product quality complaint
PVR	Pulmonary vascular resistance
QoL	Quality of Life
QS	Quality System
RHC	Right heart catheterization
RSI	Reference safety information
RVSWI	Right ventricular stroke work index
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
S-FU	Safety follow-up
SI	International System of Units
SIV	Site initiation visit
SOC	System organ class
sPAP	Systolic pulmonary artery pressure
SS	Safety analysis Set
SSG	Statistical support group
sSAP	Systolic systemic artery pressure
SM	Site Manager
SUSAR	Suspected unexpected serious adverse reaction
SV	Stroke volume
SVI	Stroke volume index
TPR	Total pulmonary resistance
ULN	Upper limit of normal
VAS	Visual analog scale
WHO	World Health Organization
WPAI©: GH	Work Productivity and Activity Impairment©: General Health

WU Wood units

PROTOCOL SYNOPSIS AC-077A301

TITLE	Prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study to compare the efficacy and safety of macitentan and tadalafil monotherapies with the corresponding fixed dose combination in subjects with pulmonary arterial hypertension (PAH), followed by an open-label treatment period with macitentan and tadalafil fixed dose combination therapy
ACRONYM	A DUE
OBJECTIVES	**Primary objective** The study has 2 co-primary objectives: 1. To evaluate the effect of the fixed dose combination (FDC) of macitentan 10 mg and tadalafil 40 mg vs macitentan 10 mg alone on pulmonary vascular resistance (PVR) at End of Double-blind Treatment (EDBT) in participants with symptomatic World Health Organization (WHO) Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with an endothelin receptor antagonist (ERA) as monotherapy. 2. To evaluate the effect of the FDC of macitentan 10 mg and tadalafil 40 mg vs tadalafil 40 mg alone on PVR at EDBT in participants with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or currently being treated with a phosphodiesterase type-5 inhibitor (PDE-5i) as monotherapy. **Secondary objectives** • To evaluate the effect of the macitentan/tadalafil (M/T) FDC compared to the respective monotherapies on: – Exercise capacity. – PAH symptoms in participants' cardiopulmonary and cardiovascular function – WHO functional class (FC). • To evaluate the safety and tolerability of the M/T FDC in the participant population. **Other objectives** Other objectives are described in Section 2.3.
DESIGN	A prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study with an open-label treatment period.

PERIODS	**Screening period:** Lasts up to 30 days; starts with the signature of the informed consent form (Visit 1) and ends the day prior to Randomization (Visit 2). **Double-blind treatment period:** Starts on the day of randomization (Visit 2) and ends on the day of the EDBT visit (Visit 8). The double-blind treatment period consists of the titration phase (the first 2 weeks) and the maintenance phase (Week 3 through Week 16). • **Titration phase:** Starts on the day of randomization (Visit 2) and lasts 2 weeks, ending the day before Visit 4 (end of Week 2). – Week 1: Loose combination 10/20: Participants are treated with a loose combination of macitentan 10 mg and/or tadalafil 20 mg and relevant placebos, depending on treatment arm, for 7 days from Randomization (Visit 2, Day 1) to the end of Week 1 (Day 7). – Week 2: Loose combination 10/40 up-titration: Participants are treated with a loose combination of macitentan 10 mg and/or tadalafil 40 mg and relevant placebos depending on treatment arm from Day 8 to the end of Week 2 (Day 14). – Note: If a participant is already receiving a stable dose of PDE-5i within prespecified dose range at baseline (ie, 40 mg tadalafil, 60 120 mg sildenafil, or 10 mg vardenafil daily), no up-titration is needed and they will receive 40 mg tadalafil from Day 1. • **Maintenance phase:** Participants are treated with macitentan 10 mg, tadalafil 40 mg, M/T FDC, or their respective placebos, depending on treatment arm. This period starts on Day 15 and lasts until the EDBT visit (Visit 8). – Note: If a participant cannot tolerate 40 mg tadalafil during the up-titration period, the participant will remain on 20 mg tadalafil. The participant is allowed to be up-titrated once again to 40 mg tadalafil during the first 2 weeks of the maintenance phase of the double-blind treatment period (ie, between Visits 4 and 5) [Section 5.1.9]. – Note: if a participant prematurely discontinues double-blind study treatment, they will be asked to return for an EDBT visit (within ±2 days of the time of treatment discontinuation and before initiation of new PAH-specific therapy), a safety follow-up visit 30 days after last treatment administration, and all remaining

visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, morbidity and mortality events, AE, and concomitant medication information will be collected. [Section 5.1.10].

Open-label treatment period[1]: For those participants who complete 16 weeks of double-blind treatment, the open-label treatment period starts with the first dose of the open-label FDC study treatment. All participants will have a titration phase of 2 weeks, during which the 2 drugs will be given as a loose combination. The open-label treatment period ends 24 months later with the End-of-Open-Label-Treatment (EOLT) visit.

- **Titration phase:**
  - First week open-label titration: Begins the first day of open-label treatment and lasts for 7 days. Participants who were randomized to the macitentan arm, or who could not tolerate 40 mg tadalafil (or corresponding placebo), in the double-blind treatment period will receive a loose combination of macitentan 10 mg and tadalafil 20 mg. Participants who were randomized to the M/T FDC or to the tadalafil monotherapy arms and who tolerated 40 mg tadalafil in the double-blind treatment period, will receive a loose combination of macitentan 10 mg and tadalafil 40 mg during this week.
  - Second week open-label titration: Begins the 8th day of open-label treatment and lasts until the 14th day of open-label treatment. All participants are treated with a loose combination of macitentan 10 mg and tadalafil 40 mg. Participants who cannot tolerate 40 mg tadalafil are not eligible to proceed to the open-label treatment period maintenance phase and should complete an End of Study (EOS) visit [see Section 8.1].
- **Maintenance phase:** Begins the 15th day of open-label treatment and ends with the EOLT visit. All participants are treated with M/T FDC.
  - Note: if a participant prematurely discontinues study treatment, they will be asked to return for an EOLT visit within ±7 days of the time of treatment discontinuation,

[1] The open label titration phase treatment assignment will be done through interactive response technology to maintain blinding of the double blind treatment period treatment.

	a safety follow-up visit 30 days after last treatment administration, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, M/M, AE, and concomitant medication information will be collected. [Section 5.1.10]. **End of Treatment (EOT):** The end of all study treatment for an individual participant. **Safety follow-up (S-FU) period:** Starts on the day after the last dose of study treatment and ends at the Safety Follow-up visit 30 35 days thereafter. For participants who completed the 24-months of open-label treatment and who are eligible for a continued access program (post-trial access program or other open-label extension study) the S-FU period will be waived. In such case enrollment into the continued access program should occur on the same day as the last visit in this study, ie, EOS visit. **End of Study (EOS):** EOS is reached when all participants have completed their EOS visit, died, or are lost to follow-up. For an individual participant, EOS visit is defined as follows: • For participants that complete treatment, EOS visit is defined as the safety follow-up visit 30 35 days after last study treatment intake. • For participants that prematurely discontinue study treatment, EOS visit is defined as either the safety follow-up visit 30 35 days after last study treatment intake or the Week 120 visit, whichever comes last. • For participants who complete treatment and who are eligible for a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOLT visit.
SUB-STUDIES	A substudy with semi-structured qualitative interviews will be conducted in selected countries among participants that have reached the open-label treatment period of the study and provided specific consent to participate in this substudy. Description of the participant experience with M/T FDC through a content analysis of the qualitative interview transcripts will be conducted separately to this study.

PLANNED DURATION	In total, including the open-label phase, approximately 54 months from first participant, first visit to last participant, last visit. In the blinded part of the study, approximately 30 months from first participant, first visit to last participant, last visit.
SITE(S) / COUNTRY(IES)	Approximately 150 sites in approximately 25 countries
PARTICIPANTS / GROUPS	170 participants are planned to be randomized into the study. Treatment allocation will be stratified by treatment status at baseline, ie, treatment-naïve or treated by an ERA or a PDE-5i as a monotherapy: • treatment-naïve participants will be randomized in a 2:1:1 ratio to M/T FDC, macitentan, or tadalafil. • participants on ERA monotherapy will be randomized in a 2:1 ratio to M/T FDC or macitentan. • participants on PDE-5i monotherapy will be randomized in a 2:1 ratio to M/T FDC or tadalafil. The sample size will be re-estimated at the interim analysis (IA) based on unblinded effect estimates, following rules as described in the IDMC charter. If the study is not terminated early for efficacy or futility, the total size of the sample shall not exceed N 250 participants and shall not be below N 150 participants, accounting for the overrun of participants recruited during the 16 weeks of follow-up.
INCLUSION CRITERIA	1. Signed and dated Informed Consent Form. 2. Male and female participants ≥18 years old. 3. Confirmed diagnosis of symptomatic PAH in WHO FC II or III. 4. Symptomatic PAH belonging to one of the following subgroups of WHO group 1 pulmonary hypertension [Simonneau 2013]: – Idiopathic. – Heritable. – Drug- or toxin-induced. – Associated with one of the following: o Connective tissue disease. o HIV infection. o Portal hypertension. o Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) with persistent pulmonary hypertension documented by a right heart catheterization (RHC) ≥1 year after surgical repair.

	5. PAH diagnosis confirmed by hemodynamic evaluation (based on central reading) at rest, evaluated within 5 weeks prior to randomization. − Mean pulmonary artery pressure ≥ 25 mmHg; AND − Pulmonary artery wedge pressure or left ventricular end diastolic pressure ≤15 mmHg; AND − PVR ≥ 3 Wood Units (ie, ≥240 dyn·sec·cm ^{5}) 6. Negative vasoreactivity test in idiopathic, heritable, and drug/toxin-induced PAH. (Patients for whom no vasoreactivity test was performed at diagnosis can be eligible if currently treated with PAH therapy for more than 3 months and PAH diagnosis confirmed by hemodynamic evaluation at least 3 months after introduction of their PAH therapy). 7. Criterion modified per Amendment 5 7.1 Currently receiving a stable dose of ERA or PDE-5i monotherapy for at least 3 months prior to baseline RHC, within the prespecified doses below or no history of PAH-specific treatment[2]: − Bosentan: 250 mg total daily dose. − Macitentan: 10 mg total daily dose. − Ambrisentan: 10 mg total daily dose. − Sildenafil: 60 120 mg total daily dose. − Tadalafil: 40 mg total daily dose. − Vardenafil: 10 mg total daily dose. 8. Participant able to perform the 6-minute walk test with a minimum distance of 100 m and maximum distance of 450 m at Screening. 9. A woman of childbearing potential is eligible only if the following applies: − Negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization. − Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation. − Agreement to follow the contraception scheme from Screening up to at least 30 days after study treatment discontinuation.
EXCLUSION CRITERIA	**PAH treatments:** 1. Treatment with a soluble guanylate cyclase stimulator, L-arginine, any form of prostanoid, or prostacyclin-receptor

[2] PAH specific treatment is defined as prostanoids, prostacyclin receptor agonists, guanylate cyclase stimulators, ERAs, or PDE 5is prescribed to treat PAH.

	agonist (including oral, inhaled, or infused routes) in the 3-month period prior to start of treatment. 2. Treatment with combination therapy of ERA and PDE-5i in the 3-month period prior to start of treatment, or history of intolerance to ERA and PDE-5i combination therapy. 3. Hypersensitivity to any of the study treatments or any excipient of their formulations. **Other therapies:** 4. Treatment with a strong cytochrome P450 (CYP) 3A4 inducer (eg, rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, or St. John's Wort) in the 1-month period prior to start of treatment. 5. Criterion modified per Amendment 3 Treatment with a strong CYP3A4 inhibitor (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, or saquinavir) or a moderate dual CYP3A4/CYP2C9 inhibitor (eg fluconazole, amiodarone) or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors in the 1-month period prior to start of treatment. 6. Treatment with doxazosin. 7. Treatment with any form of organic nitrate, either regular or intermittent. 8. Diuretic treatment initiated or dose changed within 1 week prior to the RHC or start of treatment. 9. Treatment with another investigational drug in the 3month period prior to start of treatment. **Medical history/current medical conditions:** 10. Body mass index (BMI) >40 kg/m^2 at Screening. 11. Known presence of 3 or more of the following risk factors for heart failure with preserved ejection fraction at Screening: BMI >30 kg/m^2. Diabetes mellitus of any type. Essential hypertension (even if well controlled). Coronary artery disease, ie, any of the following: o History of stable angina; or o Known more than 50% stenosis in a coronary artery; or o History of myocardial infarction; or o History of or planned coronary artery bypass grafting and/or coronary artery stenting. 12. Known presence of moderate or severe obstructive lung disease (forced expiratory volume in 1 second [FEV_1] / forced vital capacity [FVC] <70% and FEV_1 <65% of predicted after bronchodilator administration) any time prior to Screening.

	13. Known presence of moderate or severe restrictive lung disease (total lung capacity or FVC <60% of normal predicted value) any time prior to Screening. 14. Clinically significant aortic or mitral valve disease; pericardial constriction; restrictive or congestive leftsided cardiomyopathy; life-threatening cardiac arrhythmias; significant left ventricular dysfunction; or left ventricular outflow obstruction, in the opinion of the investigator 15. Known permanent atrial fibrillation, in the opinion of the investigator. 16. Known or suspected uncontrolled thyroid disease (hypo or hyperthyroidism). 17. Documented pulmonary veno-occlusive disease. **Criteria linked to macitentan/tadalafil use:** 18. Hemoglobin <100 g/L (<10 g/dL) at Screening. 19. Known severe hepatic impairment defined as a Model for End-Stage Liver Disease score ≥19.[3] 20. Serum aspartate aminotransferase and/or alanine aminotransferase >1.5 upper limit of normal (ULN) at Screening. 21. Criterion modified per Amendment 5 21.1 Severe renal impairment (Chronic Kidney Disease Epidemiology Collaboration 2009 equation [Levey 2009] calculated creatinine clearance <30 mL/min) at Screening.[4] 22. Systemic hypotension (systolic blood pressure [SBP] <90 mmHg or diastolic blood pressure [DBP] <50 mmHg) at Screening or Randomization. 23. Systemic hypertension (SBP >160 mmHg or DBP >100 mmHg) at Screening. 24. Acute myocardial infarction or cerebrovascular event (eg, stroke) within the last 26 weeks prior to Screening. 25. Known bleeding disorder, in the opinion of the investigator. 26. Loss of vision in one or both eyes because of nonarteritic anterior ischemic optic neuropathy, regardless of whether or not this episode was in connection with previous PDE5i treatment. 27. Hereditary degenerative retinal disorders, including retinitis pigmentosa. 28. History of priapism, conditions that predispose to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia), or

[3] See Section 14.8 for MELD scoring criteria.

[4] Calculated creatinine clearance is measured as eGFR in this study (Section 7.2.4.2).

	anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie's disease). **General restrictions:** 29. Difficulty swallowing large pills/tablets that would interfere with the ability to comply with study treatment regimen. 30. Any planned surgical intervention (including organ transplant) during the double-blind treatment period, except minor interventions. 31. Exercise training program for cardiopulmonary rehabilitation in the 12-week period prior to start of treatment, or planned to be started during the double-blind period of the study. 32. Pregnant, planning to become pregnant, or lactating. 33. Any known factor or disease that might interfere with treatment adherence, study assessments, study conduct, or interpretation of the results as judged by the investigator (eg, drug or alcohol dependence, psychiatric disease, use of walking aids, etc.). 34. Known concomitant life-threatening disease with a life expectancy <12 months. **Other therapies:** 35. Criterion added per Amendment 5 Calcium channel blocker treatment initiated, or dose changed within 3 months prior to RHC at screening.
STUDY TREATMENTS	**Investigational treatment** M/T FDC will be provided as film-coated tablets. The doses of macitentan (10 mg) and tadalafil (40 mg) selected for the M/T FDC are those recommended for each compound and correspond to the doses used for monotherapy. **Comparator** Monotherapy arms of macitentan 10 mg and tadalafil 40 mg (2 × 20 mg tablets). Matching placebo tablets will not contain any active substance but are otherwise identical in appearance to the respective active drug tablet.
ENDPOINTS	**Primary efficacy endpoint** • Change in PVR expressed as the ratio of the geometric means of EDBT to baseline. **Secondary efficacy endpoints** The secondary efficacy endpoints are:

	• Change from baseline to EDBT in 6-minute walk distance. • Change from baseline to Week 16 in PAH-Symptoms and Impact™ (PAH-SYMPACT™) in Cardiopulmonary symptom domain score • Change from baseline to Week 16 in PAH-SYMPACT™ in Cardiovascular symptom domain score • Proportion of participants with absence of worsening in WHO FC from baseline to EDBT. **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Safety endpoints** Safety endpoints for the double-blind and open-label treatment periods are: • Treatment-emergent adverse events (AEs). • Serious adverse events (SAEs). • Deaths. • AEs leading to premature discontinuation of study treatment. • Change in vital signs (SBP and DBP and pulse rate) and body weight from baseline to all assessed time points during the study. • Treatment-emergent marked laboratory abnormalities. • Proportion of participants with a treatment-emergent ALT and/or AST abnormality (≥3, ≥5, and ≥8 × ULN). • Proportion of participants with a treatment-emergent ALT and/or AST abnormality (≥3 × ULN) associated with total bilirubin ≥2 × ULN (and increased as compared to baseline). • Proportion of participants with a treatment-emergent hemoglobin abnormality (<100 g/L, and <80 g/L). • Treatment-emergent AEs of special interest (hypotension, anemia, edema, liver events).
ASSESSMENTS	Refer to the schedule of assessments in Section 7.
STATISTICAL METHODOLOGY	This study implements an adaptive group-sequential design with early futility and efficacy stopping rules and sample size re-estimation. It includes an IA (according to group-sequential design methodology) when approximately 100 participants have completed their Week 16 assessment or have discontinued the study prior to their Week 16 assessment and after the global amendment 5 has been approved in all the countries. **Analysis sets**

	The All Randomized Analysis Set includes all participants who were randomized in the study. The Full Analysis Set (FAS) includes all participants assigned to a study treatment who received at least one dose (for participants in FDC at least one dose of either macitentan or tadalafil) of study treatment. The Safety Set includes all participants who received at least one dose of study treatment in the double-blind treatment period. The Combination Safety Set includes all participants randomized to M/T FDC in the double-blind period who received at least one dose of M/T FDC double-blind study treatment and received at least one dose of M/T FDC study treatment in the open-label period. The PAH-SYMPACT™ Symptoms Analysis Set includes all participants included in the FAS for whom at least one baseline value of symptoms domain is provided. The PAH-SYMPACT™ Impacts Analysis Set includes all participants included in the FAS for whom at least one baseline value of impacts domain is provided. **Primary endpoint analysis** The primary endpoint will be tested on the FAS (including imputed EDBT PVR values when applicable) using 2 analysis of covariance (ANCOVA) models separately comparing the combination group to each monotherapy. The primary estimand targets an "on-treatment" estimate of the treatment differences between M/T FDC and each monotherapy arm. Specifically, assessments obtained after introduction of prohibited PAH therapy or study treatment discontinuation/interruption for more than 2 days immediately prior to the EDBT visit are not included in the primary analysis (will be imputed). Each null hypothesis will be tested at the alpha level as determined by the Hwang, Shih and DeCani alpha spending function with gamma (γ) 2 dependent on the information fraction at the time of the IA. Only if both are rejected will the study be declared to show conclusive evidence of efficacy. The overall alpha is controlled so as not to exceed 5%. The null hypotheses will be tested by means of 2 ANCOVA models on the $\log_e$-transformed ratios of EDBT to baseline PVR values. Model covariates will include randomized treatment, the

	log_e-transformed baseline PVR value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i). The resulting least squares means (LS-means) and 95% confidence limits (CLs) obtained in each treatment group and the LS-means differences (95% CLs) for M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg will be inversely transformed using the exponential function and multiplied by 100 to provide: 1. the adjusted geometric mean of the ratios of EDBT to baseline PVR values and corresponding 95% CLs, expressed as a percentage, in each treatment group, and; 2. the adjusted geometric mean ratios (GMRs) and corresponding 95% CLs for M/T FDC vs macitentan 10 mg (GMR1) and for M/T FDC vs tadalafil 40 mg (GMR2). The global null hypothesis will be rejected if the p-values from each test are less than the alpha allocated at the time of the IA or, if the study is not stopped at the time of the IA, less than the remaining alpha at the time of the final analysis. Median unbiased parameter estimates and repeated CLs will be presented in the final analysis. **Secondary variables** The secondary efficacy variables will be analyzed at the same alpha level as the primary endpoint using a hierarchical testing procedure following the order specified in the secondary endpoints [Section 10.3.3]. **Safety variables** Treatment-emergent AEs, SAEs, deaths, AEs leading to permanent discontinuation of study treatment, AEs of special interest, and laboratory marked abnormalities will be summarized by frequency tables. Change from baseline in vital signs and body weight will be summarized for each scheduled visit. Safety variables will be presented for the double-blind treatment period on the Safety Set and separately for the entire FDC treatment period (ie, for participants treated with M/T FDC either in the double-blind or open-label period) on the Combination Safety Set (CSS). **Subgroup analyses** In order to assess the consistency of the treatment effect across different participant subgroups, analyses will be performed on the primary and secondary efficacy variables classifying participants according to relevant demographic characteristics. The subgroups to be considered are: • Geographical region (eg, US, Europe, Asia).

- Region (US, non-US).
- WHO FC (II vs III).

Treatment-by-subgroup interaction will be investigated by means of tests of heterogeneity.

In addition, the treatment effects of:

- M/T FDC vs each monotherapy arm will be assessed in the treatment-naïve stratum only;
- M/T FDC vs tadalafil 40 mg will be assessed in the prior-PDE-5i stratum only; and
- M/T FDC vs macitentan 10 mg will be assessed in the prior-ERA stratum only.

Interim analysis

One IA will be conducted when approximately 100 participants have either completed their Week 16 assessment or have discontinued from the study prior to their week 16 assessment. The IA will only include data from countries in which the global amendment 5 has been approved.

The IA will be conducted on the primary endpoint to allow for early study termination due to overwhelming efficacy or futility, and for adaptive sample size re-estimation (to between 150 and 250 participants) if the study is not terminated. The Independent Data Monitoring Committee (IDMC) will review the interim results and make corresponding recommendations in line with the IDMC charter. The independent statistical support group (SSG) will perform the IA and make unblinded results available to the IDMC.

Following the IA, recruitment will be stopped if futility or superiority is demonstrated. In the event the study is stopped for futility, all participants will be requested to return for an EOT visit and be transitioned to system organ class (SOC). In the event the study is stopped for efficacy, all participants in the double-blind treatment period will be requested for a EDBT visit and transitioned to the open-label treatment, participants already enrolled in the open-label period of the study will be allowed to continue through the end of the open-label treatment period. In the case the IA results in early study stop, RHC at EDBT will not be required for this study for participants after IA decision, however if RHC is done as SOC, results should be recorded in the eCRF.

Sample size

The trial will enroll between 150 and 250 participants.

	Sample size is calculated based on the statistical requirements for detection of a clinically relevant difference between the FDC group and both monotherapy groups using a 2:1 randomization ratio for each pairwise comparison and taking into account an IA with unblinded sample size re-estimation. Each test comparing the FDC to a monotherapy arm has a two-sided Type I error of 5% and a Type II error of 13% (87% power). The following assumptions are made: • The effect, as measured by the ratio of geometric means of the EDBT / baseline PVR values for FDC compared to the most efficient of the 2 monotherapies is assumed to be 0.75, and to be consistent across the treatment-naïve, prior-ERA, and prior-PDE-5i strata. • A coefficient of variation of the ratio of 0.45. • One interim analysis is planned using an alpha spending function from the Hwang, Shih and DeCani class with (γ) 2. • Normal distribution for the $\log_e$-transformed ratio of EDBT to baseline PVR values. Given those assumptions, 170 participants are targeted to be randomized overall into the trial. Depending on the conditional power at the IA, the sample size can be re-calculated to between 150 and 250 participants.
STUDY COMMITTEES	A Steering Committee has been appointed by the sponsor to oversee conduct of the study. An IDMC has overall responsibility for safeguarding the interests of participants by monitoring unblinded safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC will interpret the results of the planned IA performed by the independent SSG as outlined in Section 10.4. The IDMC and independent SSG will be fully operational prior to enrollment of the first participant into the study. The composition and operation of the IDMC is described in the IDMC charter. An independent Clinical Events Committee of PAH experts will review and confirm all reported mortality and morbidity events, including start date of the event, in a blinded fashion. An Independent Liver Safety Data Review Board (an external expert committee of hepatologists) has been appointed to monitor all studies with macitentan, and to provide ongoing assessment and

	advice regarding serious hepatic AEs of special interest that require further evaluation during the study.

PROTOCOL

1 BACKGROUND

1.1 Indication

1.1.1 Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a serious chronic disorder of the pulmonary circulation of diverse etiology and pathogenesis. PAH is characterized by a progressive increase in pulmonary arterial pressure (PAP) and in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death [Benza 2010, Kylhammar 2014, Tonelli 2013]. The complex pathogenesis of PAH involves dysfunction of 3 key pathways: the endothelin pathway, the nitric oxide pathway, and the prostacyclin pathway [Humbert 2004].

PAH is currently hemodynamically characterized by a resting mean pulmonary arterial pressure (mPAP) of at least 25 mmHg with normal pulmonary artery wedge pressure (PAWP; or left ventricular end-diastolic pressure [LVEDP]) of 15 mmHg or less, and a PVR greater than 3 Wood Units (WU) [Hoeper 2013].

The 2013 clinical classification of pulmonary hypertension [Simonneau 2013] classifies the numerous conditions that are known to lead to or be associated with the development of PAH into 4 groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause / associated etiology (idiopathic), in a familial setting (heritable), or as the result of the use of certain drugs or toxins, or it can be associated with a connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.

1.1.2 Current treatment practice

Current PAH-specific therapeutic options include treatments that target the 3 pathways mentioned above (endothelin, nitric oxide, and prostacyclin pathways). Many patients, in accordance with current treatment guidelines, are treated with combination therapies to target multiple pathways at once [Sitbon 2016; Galiè 2015a].

Recent studies have supported the efficacy of both initial and sequential combination therapy. Data from the pivotal Phase 3 study that demonstrated the safety and efficacy of macitentan compared to placebo (SERAPHIN) support the benefits of combination therapy. Approximately 64% of participants in this study received a background PAH therapy, either phosphodiesterase type-5 inhibitors (PDE-5is; 96.4% of those on background therapy) or oral or inhaled prostanoids (8.5% of those on background therapy). Based on a sub-analysis of SERAPHIN data, participants on combination therapy (ie, macitentan and background PAH therapy) showed a 38% reduced risk of morbidity/mortality (M/M) compared to participants on background PAH therapy alone (hazard ratio: 0.62, 95% confidence interval [CI] 0.49 0.89, p 0.009, n 154) [Jansa 2018].

Benefits of the combination of an endothelin receptor antagonist (ERA) and a PDE-5i were further demonstrated in a study with the ERA ambrisentan and the PDE-5i tadalafil (AMBITION trial) comparing the up-front combination of both drugs vs monotherapy with ambrisentan or PDE-5i. This study showed a benefit with a 50% relative reduction on a composite endpoint of clinical

failure events (ie, death, hospitalization, PAH progression, and unsatisfactory clinical status) for the combination therapy group vs the pooled monotherapy group (95% CI 0.35 0.72; p <0.001) [Galiè 2015b].

While combination treatment is common, fixed-dose combination (FDC) pills or tablets that combine 2 or more PAH-specific therapies are not available, thereby requiring patients to take multiple pills/tablets daily.

1.2 Study Treatment(s)

1.2.1 Macitentan/Tadalafil FDC

ACT-064992D is an FDC of macitentan (ACT-064992) 10 mg and tadalafil 40 mg in one film-coated tablet, to be administered orally once daily (o.d.).

1.2.1.1 Nonclinical results of combination macitentan and tadalafil

To test the effect of the combination of macitentan and tadalafil vs macitentan alone and tadalafil alone, the acute hemodynamic effects of combined treatment with macitentan and tadalafil were investigated in conscious Dahl-S and spontaneously hypertensive rats, 2 animal models of systemic hypertension associated with endothelial dysfunction. The results demonstrated a synergistic hemodynamic effect of macitentan and tadalafil in combination.

To confirm that the synergism observed in hypertensive rats could also apply to pulmonary hypertension, the effect of the combination of macitentan and tadalafil vs macitentan alone and tadalafil alone was investigated in conscious hypoxia / Sugen 5416 rats. Single-dose oral administration of the individual monotherapies vs combination therapy showed a decreased mPAP with combination therapy equal to the sum of the effect of each monotherapy and an area between the treatment vs time-control curves greater than the sum of each monotherapy. These results indicate an additive/synergistic effect on pulmonary hemodynamics.

Based on these data, it was concluded that compared to monotherapy, the combination of macitentan and tadalafil provides a benefit to pulmonary hemodynamics in a well-established rat model of pulmonary hypertension without increasing the risk of exaggerated systemic vasodilation, ie, without increasing the risk of systemic hypotension. Taken together with the previous studies performed in rats with systemic hypertension, the data demonstrate that the combination of macitentan and tadalafil provides selective benefits in vascular territories associated with endothelial dysfunction.

For non-clinical results specific to the 2 constituent monotherapies, please refer to Section 1.2.2.1, Section 1.2.3.1, and the Investigator's Brochure (IB) [Macitentan/tadalafil FDC IB].

1.2.1.2 Clinical pharmacology of combination macitentan and tadalafil

In total, over 160 healthy participants were treated with macitentan/tadalafil (M/T) FDC in 2 Phase 1 trials to show bioequivalence between the loose combination of monotherapies and FDC. The M/T FDC was well tolerated in both studies. The most frequently reported adverse event (AE) was headache [Macitentan/tadalafil FDC IB].

For clinical pharmacology specific to the 2 constituent monotherapies, please refer to Section 1.2.2.2, Section 1.2.3.2, and the Investigator's Brochure [Macitentan/tadalafil FDC IB].

1.2.1.3 Clinical efficacy of combination macitentan and tadalafil

To date, there is no clinical experience with the M/T FDC (ie, the combination given as a single tablet) in PAH patients. Clinical efficacy has been established for both of the constituent monotherapies alone [Section 1.2.2.3, Section 1.2.3.4, Macitentan/tadalafil FDC IB].

In the OPTIMA study, an ongoing open-label Phase 4 study in which newly diagnosed PAH patients in World Health Organization (WHO) functional class (FC) II III receive macitentan 10 mg and tadalafil 40 mg o.d. (administered as a loose combination), efficacy data from the first 30 participants who completed 16 weeks of treatment indicate a substantial decrease of PVR (reduced by 51% from baseline [95% CI 44, 57]) and N-terminal pro B-type natriuretic peptide (NT-proBNP; reduced by 78% from baseline [95% CI 64, 88]), and a numerical increase in 6-minute walk distance (6MWD; mean increase of 31 m from baseline [95% CI 1, 64]). None of the participants had a worsening of WHO functional class [Macitentan/tadalafil FDC IB].

1.2.1.4 Summary of safety profile of combination macitentan and tadalafil

The safety of the M/T FDC (ie, the combination given as a single tablet) in patients with PAH has not been established. Summaries of the safety profiles of the constituent monotherapies are provided in Sections 1.2.2.4 and 1.2.3.4

In Phase 1 studies with healthy volunteers, M/T FDC was well tolerated.

In OPTIMA, at the interim analysis (IA) of the first 30 participants, 80% of participants had at least 1 AE and 13.3% (4 participants) had at least 1 serious adverse event (SAE). The most frequently reported AEs were headache (in 27%) and peripheral edema (in 17%). The information from this IA suggest that the co-administration of macitentan 10 mg and tadalafil 40 mg was well tolerated. The data did not indicate any specific tolerability or safety concerns [Macitentan/tadalafil FDC IB].

1.2.2 Macitentan

Macitentan is approved in the US, the EU, and an increasing number of other countries for the treatment of PAH [Opsumit® SmPC, Opsumit® USPI].

1.2.2.1 Non-clinical results of macitentan

Macitentan is an orally active, non-peptide, potent dual endothelin receptor A and B antagonist. Macitentan showed dose-dependent efficacy in nonclinical models of systemic hypertension and pulmonary hypertension. In nonclinical safety studies, no effects on normal physiological functions or electrocardiogram (ECG) variables including cardiac repolarization were observed, with the exception of a decrease in systemic arterial blood pressure observed in a cardiovascular study in dogs. Macitentan has no genotoxic and no carcinogenic potential. In the pivotal 26-week and 39-week toxicity studies, the exposures in animals at the no-observed-adverse-effect levels were above the anticipated clinical exposures and provided a margin of safety for studies in humans. Reproductive toxicity studies showed that macitentan is teratogenic. Teratogenicity is considered to be an ERA class effect. Like other ERAs, macitentan may have an adverse effect on spermatogenesis [Opsumit® USPI].

1.2.2.2 Clinical pharmacology of macitentan

During the Phase 1 program, more than 200 healthy participants, 24 participants with hepatic impairment, and 8 participants with renal impairment were treated with macitentan. Macitentan was well tolerated in all studies. The most frequently reported AE was headache [Opsumit® USPI; Macitentan/tadalafil FDC IB].

1.2.2.3 Clinical efficacy of macitentan

Efficacy was established in the SERAPHIN study, a long-term study in 742 PAH patients with predominantly WHO FC II III symptoms treated for an average of 2 years [Pulido 2013]. 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 PDE-5is or inhaled prostanoids.

The trial demonstrated that macitentan 10 mg reduces the risk of M/M in patients with symptomatic PAH, with a hazard ratio vs placebo of 0.55, 97.5% confidence limits (CLs): 0.39, 0.76, p <0.001. This represents a risk reduction of 45% [Pulido 2013]. The effect of macitentan was observed regardless of whether the patient was receiving another therapy, including a PDE-5i, for PAH.

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 substudy in 187 participants 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].

1.2.2.4 Summary of safety profile of macitentan

The safety of macitentan has been evaluated in a long-term placebo-controlled trial of 742 patients with symptomatic PAH, the SERAPHIN study [Pulido 2013, Macitentan/tadalafil FDC IB]. 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 overall incidence of treatment discontinuations because of adverse events was similar across macitentan 10 mg and placebo treatment groups (approximately 11%).

1.2.3 Tadalafil

Tadalafil is approved in the US [Adcirca® USPI], the European Union [Adcirca® SmPC], and many other countries (see local prescribing information) for the treatment of PAH.

1.2.3.1 Non-clinical results of tadalafil

Tadalafil is a selective inhibitor of phosphodiesterase type-5 (PDE-5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE-5 is the predominant

phosphodiesterase in the pulmonary vasculature. Inhibition of PDE-5 by tadalafil increases the concentrations of cGMP, resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed [Adcirca® USPI].

1.2.3.2 Clinical pharmacology of tadalafil

In clinical pharmacology studies, tadalafil (5 20 mg) was shown to potentiate the hypotensive effect of nitrates. Tadalafil must not be used in patients taking any form of organic nitrates [Adcirca® SmPC].

For other pharmacodynamics effects, interactions, and the pharmacokinetics of tadalafil, see the Summary of Product Characteristics and US Prescribing Information [Adcirca® SmPC, Adcirca® USPI].

1.2.3.3 Clinical efficacy of tadalafil

Tadalafil was evaluated in a Phase 3, randomized, double-blind, 16-week placebo-controlled study conducted in 405 patients with PAH [Galiè 2009]. Allowed background therapy included bosentan (maintenance dosing up to 125 mg twice daily), which, like macitentan, is a dual endothelin receptor A and B antagonist. Participants were randomly assigned to 1 of 5 treatment groups (tadalafil 2.5, 10, 20, or 40 mg, or placebo) in a 1:1:1:1:1 ratio. PAH etiologies were predominantly idiopathic PAH (61%) and related to collagen vascular disease / connective tissue disorders (24%). More than half (53%) of the participants in the study were receiving concomitant bosentan therapy. The majority of participants had a WHO FC III (65%) or II (32%). The mean baseline 6MWD was 343 m. The primary efficacy endpoint was the change from baseline at Week 16 in 6MWD. In the tadalafil 40 mg treatment group, the placebo-adjusted mean increase in 6MWD was 33 m (95% CI: 15 50 m; p <0.001). There was increased time to and decreased incidence of clinical worsening (p 0.04) (defined as death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy, or worsening WHO FC) in the tadalafil 40 mg group compared to the placebo group and the groups that used lower doses of tadalafil.

1.2.3.4 Summary of safety profile of tadalafil

In the pivotal placebo-controlled study of tadalafil for the treatment of PAH, a total of 323 patients were treated with tadalafil at doses ranging from 2.5 mg to 40 mg o.d. and 82 patients were treated with placebo. The duration of treatment was 16 weeks. The overall frequency of discontinuation due to AEs was low (tadalafil 16%, placebo 16%). The most commonly reported adverse reactions, occurring in ≥10% of patients in the tadalafil 40 mg treatment arm, were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharyngitis, and pain in extremity. The adverse reactions reported were transient and generally mild or moderate. [Adcirca® USPI, Macitentan/tadalafil FDC IB].

1.3 Purpose and Rationale of the Study

Study purpose

This study is a Phase 3 clinical study to demonstrate that M/T FDC is superior to 10 mg of macitentan alone, and to 40 mg of tadalafil alone, as measured by the change from baseline in PVR at End of Double-Blind Treatment (EDBT).

Study rationale

PAH continues to be a progressive and fatal disease, with a life expectancy of only about 7 10 years, despite the availability of PAH-specific therapies [Benza 2012a; Fares 2016]. ERAs and PDE-5is are the most widely used therapies for PAH. The safety and efficacy of oral combination therapy with ERAs and PDE-5is have been the participant of active investigation for more than a decade, with the benefit of targeting different pathways known to be involved in the pathogenesis of the disease [Sitbon 2016]. The 2015 European Treatment Guidelines provide recommendations for the use of initial or sequential combination therapy, according to WHO FC [Galiè 2015a].

Adherence to prescribed therapy has an impact on clinical outcomes and there is strong evidence that reducing the pill/tablet count and frequency has a major impact on patients' adherence to therapies in general and to PAH therapies in particular [Thom 2013]. One way to simplify treatment is to use FDC products that combine multiple treatments into a single tablet.

This study will evaluate the efficacy and safety at 16 weeks of an FDC, macitentan 10 mg and tadalafil 40 mg, against either of these 2 PAH-approved therapies given as monotherapy to further confirm the added value of the FDC.

Study description

This is a prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study with a double-blind treatment period duration of 16 weeks followed by a 24-month single-arm open-label extension period.

1.4 Summary of Known and Potential Risks and Benefits

1.4.1 Benefits

An FDC is an attractive option for PAH patients because it simplifies the treatment regimen by combining 2 therapies (which would otherwise involve a total of 3 tablets: one macitentan 10 mg tablet and 2 tadalafil 20 mg tablets) into a single tablet. This therapeutic approach is consistent with the European Society of Cardiology and the European Respiratory Society treatment guidelines and with clinical practice, which favor combination therapy in order to target separate signaling pathways known to be involved in the pathogenesis of the disease. The efficacy of the 2 component medications administered individually, macitentan and tadalafil, in adult patients with symptomatic PAH has been demonstrated in randomized clinical trials.

The efficacy of the loose combination of macitentan 10 mg / tadalafil 40 mg is being evaluated in the ongoing open-label OPTIMA trial. An analysis of the first 30 participants to complete 16 weeks of treatment with macitentan and tadalafil showed a substantial decrease of PVR and NT-proBNP, and a numerical increase in 6MWD. FC improved in the majority of these first 30 participants [Macitentan/tadalafil FDC IB].

1.4.2 Possible risks

The safety profiles of ERAs and PDE5i administered either as mono- or combination therapy in PAH patients have been well characterized through relatively large event-driven clinical trials such as SERAPHIN and PHIRST. Based on the known characteristics of macitentan and tadalafil, no pharmacokinetic interaction is expected when administered concomitantly.

Known safety concerns associated with ERA treatment include hepatic events, hemoglobin decrease, and embryo-fetal toxicity. Known safety concerns associated with PDE-5i treatment include hypotension, visual loss, hearing loss, and priapism [Macitentan/tadalafil FDC IB]. With regard to the specific combination of macitentan and tadalafil, the Phase 1 studies assessing the pharmacokinetics of the M/T FDC yielded a high reporting rate of headache in healthy volunteers, similar to the loose combination and the FDC formulations, but no concerns arose regarding blood pressure or other safety measures.

In the AMBITION study, which compared initial combination therapy with the ERA ambrisentan and tadalafil versus monotherapy (ie, ambrisentan or tadalafil), AEs of peripheral edema, headache, nasal congestion, and anemia were more common in the combination therapy group than in either monotherapy group [Galiè 2015b]. Preliminary data from an ongoing study (OPTIMA), where the up-front loose combination of macitentan 10 mg and tadalafil 40 mg is administered to PAH patients, did not indicate any tolerability or safety concerns specific to combination treatment [Macitentan/tadalafil FDC IB].

The following measures are being taken to minimize the risks for the participants participating in the study:

- Exclusion of potential participants with increased liver function test (LFT) values or decreased hemoglobin values [Section 4.4].
- Regular monitoring of LFTs [Section 7.2].
- Exclusion of women of childbearing potential who are unable or unwilling to comply with study-mandated contraception methods [Section 4.3].
- Close monitoring of the study by an external Independent Data Monitoring Committee (IDMC) throughout the study [Section 3.4].
- Regular physical examination during the study [Section 7.2].
- Regular vital sign checks during the study [Section 7.2].

1.4.3 Benefit/risk analysis

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

Given the extensive and long-term controlled efficacy and safety data available for macitentan and tadalafil individually, in addition to the extensive available post-marketing surveillance data, and the careful follow-up of participants mandated by this protocol, the benefit/risk analysis supports the current study.

2 STUDY OBJECTIVES

2.1 Primary Objective

This study has 2 co-primary objectives:

1. To evaluate the effect of the M/T FDC vs macitentan 10 mg alone on PVR at EDBT in participants with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with an ERA as monotherapy.
2. To evaluate the effect of the M/T FDC vs tadalafil 40 mg alone on PVR at EDBT in participants with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naïve or are currently being treated with a PDE-5i as monotherapy.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effect of the M/T FDC compared to the respective monotherapies on:
  - Exercise capacity.
  - PAH symptoms in participants' cardiopulmonary and cardiovascular function
  - WHO FC.
- To evaluate the safety and tolerability of the M/T FDC in the participant population.

2.3 Other Objectives

Other objectives for the 16-week double-blind treatment period are:

- To evaluate the effect of the M/T FDC compared to the respective monotherapies on:
  - PAH impacts on participants' physical and cognitive/emotional functions.
  - Time to first M/M event.
  - Time to death due to PAH or PAH-related hospitalization.
  - Other hemodynamic measures.
  - Participant's quality of life (QoL).
  - Participant's work and productivity.
  - Pharmacoeconomic measures.
  - Time to death (all causes)

Other objectives for the 24-month open-label treatment period are:

- To evaluate the long-term safety of the M/T FDC.
- To evaluate the long-term effect of the M/T FDC on: Exercise capacity.
  - WHO FC.
  - Time to first M/M event.
  - Time to death due to PAH or PAH-related hospitalization.
  - Pharmacoeconomic measures.

  Time to death (all causes)

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study Design

This is a prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study with a treatment period duration of 16 weeks followed by a 24-month single-arm open-label treatment period. In the double-blind

treatment period, the FDC of macitentan 10 mg and tadalafil 40 mg is compared to each monotherapy of macitentan 10 mg or tadalafil 40 mg given o.d.

In total, 170 participants are planned to be randomized into the study (range 150 250) to receive either M/T FDC, macitentan 10 mg, or tadalafil 40 mg given o.d. Participants will also receive matching placebos for the 2 other study treatments to maintain the blind. Treatment allocation will be stratified by treatment status at baseline, ie, treatment-naïve or treated by an ERA or a PDE-5i as a monotherapy:

- treatment-naïve participants will be randomized in a 2:1:1 ratio to M/T FDC, macitentan, or tadalafil.
- participants on allowed ERA monotherapy will be randomized in a 2:1 ratio to M/T FDC or macitentan.
- participants on allowed PDE-5i monotherapy will be randomized in a 2:1 ratio to M/T FDC or tadalafil.

After completion of the double-blind treatment period, participants will continue the study in an open-label treatment period for 24 months, during which all participants will receive M/T FDC. All EDBT assessments must be completed before the participant enters the open-label treatment period.

The study will be conducted in approximately 150 sites in approximately 25 countries.

An IA will be conducted when approximately 100 participants have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16. The IA will only include data from countries in which the global amendment 5 has been approved.

The recruitment rate will be closely monitored in a blinded manner to ensure there are at least 50% participants in treatment-naïve stratum at the time of the final analysis.

This analysis can allow for early termination for efficacy or futility, or unblinded reassessment of sample size required for the primary endpoint. Following the IA, recruitment will be stopped if futility or superiority is demonstrated. In the event the study is stopped for futility, all participants will be requested to return for an EOT visit and be transitioned to system organ class (SOC). In the event the study is stopped for efficacy, all participants in the double-blind treatment period will be requested for a EDBT visit and transitioned to the open-label treatment, participants already enrolled in the open-label period of the study will be allowed to continue through the end of the open-label treatment period. In the case the IA results in early study stop, right heart catheterization (RHC) at EDBT will not be required for this study for participants after IA decision, however if RHC is done as standard of care, results should be recorded in the eCRF.

3.1.1 Study periods

The study comprises the following consecutive periods:

Screening period: Lasts up to 30 days; starts with the signature of the Informed Consent Form (ICF; Visit 1) and ends the day prior to randomization (Visit 2).

Double-blind treatment period: Starts on the day of randomization (Visit 2) and ends on the day of the EDBT visit (Visit 8).

The double-blind treatment period consists of the titration phase (the first 2 weeks) and the maintenance phase (Week 3 through Week 16).

- **Titration phase:** Starts on the day of randomization (Visit 2, Day 1) and lasts 2 weeks, ending on Day 14 (end of Week 2).
  - Week 1: Loose combination 10/20: Participants are treated with a loose combination of macitentan 10 mg and/or tadalafil 20 mg and relevant placebos, depending on treatment arm, for 7 days from randomization (Visit 2, Day 1) to the end of Week 1 (Day 7).
  - Week 2: Loose combination 10/40 Uptitration: Participants are treated with a loose combination of macitentan 10 mg and/or tadalafil 40 mg and relevant placebos depending on treatment arm from Day 8 to the end of Week 2 (Day 14).
  - Note: If a participant is already receiving a stable dose of PDE-5i within prespecified dose ranges at baseline (ie, 40 mg tadalafil, 60 120 mg sildenafil, or 10 mg vardenafil daily), no up-titration is needed and they will receive 40 mg tadalafil from Day 1.
- **Maintenance phase:** Participants are treated with macitentan 10 mg, tadalafil 40 mg, M/T FDC, or their respective placebos, depending on treatment arm. The period starts on Day 15 and lasts until EDBT (Visit 8).
  - Note: If a participant cannot tolerate 40 mg tadalafil during the titration period, the participant will remain on 20 mg tadalafil. The participant is allowed to be up-titrated once again to 40 mg tadalafil during the first 2 weeks of the maintenance phase of the double-blind treatment period (ie, between Visits 4 and 5) [Section 5.1.9].
  - Note: if a participant prematurely discontinues double-blind study treatment, they will be asked to return for a EDBT visit (within ±2 days of the time of treatment discontinuation and before initiation of new PAH-specific therapy), a safety follow-up visit 30 days after last treatment administration, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, morbidity and mortality events (M/M) AE, and concomitant medication information will be collected [Section 5.1.10].

Open-label treatment period: For those participants who complete 16 weeks of double-blind treatment, the open-label treatment period starts with the first dose of the open-label FDC study treatment. All participants will have a titration phase of 2 weeks, during which the 2 drugs will be given as a loose combination. The open-label treatment period lasts at least 24 months and ends with the End-of-Open-Label-Treatment (EOLT) visit. Participation in the open-label treatment period may be prolonged beyond 24 months until macitentan and tadalafil are accessible at the required doses, through other options according to local regulations. Refer to Section 8.1 for definition of study completion and Section 8.4 for details of continued access to study intervention.

- **Titration phase[5]:** Starts on the first day of open-label treatment and lasts for 2 weeks.
  - First week open-label titration: Begins the first day of open-label treatment and ends the 7th day of open-label treatment. Participants who received macitentan monotherapy, or could not tolerate 40 mg tadalafil, in the double-blind treatment period will receive a loose combination of macitentan 10 mg and tadalafil 20 mg. Participants who had received the M/T FDC or tadalafil monotherapy treatment and could tolerate 40 mg tadalafil in the double-blind treatment period, will receive a loose combination of macitentan 10 mg and tadalafil 40 mg during this week.
  - Second week open-label titration: Begins the 8th day of open-label treatment and ends on the 14th day of open-label treatment. All participants are treated with a loose combination of macitentan 10 mg and tadalafil 40 mg. Participants who cannot tolerate 40 mg tadalafil are not eligible to proceed to the open-label treatment period maintenance phase and should complete an End of Study (EOS) visit [see Section 8.1].
- **Maintenance phase:** Begins the 15th day of open-label treatment and ends with the EOLT. All participants are treated with M/T FDC.
  - Note: if a participant prematurely discontinues study treatment, they will be asked to return for an EOLT visit within ±7 days of the time of treatment discontinuation and a safety follow-up visit 30 days after last treatment administration. If the participant did not withdraw consent for study participation, regular contacts will be conducted thereafter, at the scheduled visits until the Week 120 visit. If regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, morbidity and mortality events (M/M) AE, and concomitant medication information will be collected [Section 5.1.10].

End-of-Treatment (EOT): For an individual participant is the end of all study treatment.

Safety follow-up (S-FU) period: Starts on the day after the last dose of study treatment and ends at the Safety Follow-up Visit 30 35 days thereafter.

For participants who completed the 24-months of open-label treatment and who are eligible for a continued access program (post-trial access program or other open-label extension study) the S-FU period will be waived. In such case enrollment into the continued access program should occur on the same day as the last visit in this study, ie, EOS visit.

End of Study (EOS): EOS is reached when all participants have completed their EOS visit, died, or are lost to follow-up.

For an individual participant, EOS visit is defined as follows:

For participants who complete treatment, EOS visit is defined as the safety follow-up visit 30 35 days after last study treatment intake.

For participants who complete treatment and who are eligible for a continued access program (post-trial access or other open-label extension study) the EOS visit is defined as the EOLT visit.

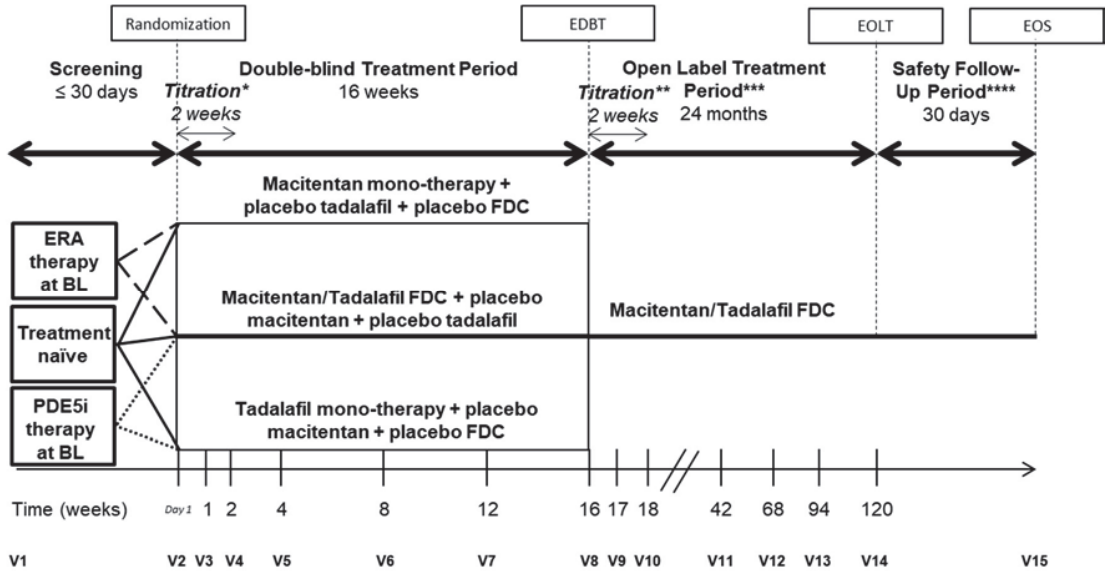
[5] The open label titration phase treatment assignment will be done through Interactive Response Technology (IRT) to maintain blinding of the double blind treatment period treatment.

For participants who prematurely discontinue study treatment, EOS visit is defined as either the safety follow-up visit 30 35 days after last study treatment intake or the Week 120 visit, whichever comes last.

The visit schedule and protocol-mandated procedures are performed according to the tables of assessments [Table 4 and Table 5] and are described in Section 7.

The overall study design is depicted in Figure 1.

Figure 1 Study design



BL baseline; EDBT End of Double blind Treatment; EOLT End of Open Label Treatment; EOS End of Study; ERA endothelin receptor antagonist; FDC fixed dose combination; IRT Interactive Response Technology; LC loose combination; M/T FDC macitentan/tadalafil FDC; PDE 5i Phosphodiesterase type 5 inhibitor; V visit.

* Participants who were on an allowed dose of PDE 5i at baseline (40 mg tadalafil, 60 120 mg sildenafil, or 10 mg vardenafil daily) will not up titrate and will receive 40 mg tadalafil starting on study Day 1. If a participant cannot tolerate the higher tadalafil dose (or placebo) during the double blind titration phase, the dose will be decreased back to 20 mg daily. Within the first 2 3 weeks after decreasing the dose (up to and including Week 4 / Visit 5) and with the investigator's approval, the participant is allowed to be re uptitrated to the tadalafil 40 mg daily dose (or its matching placebo equivalent). If the participant cannot tolerate the 40 mg dose again on the 2nd attempt to up titrate the tadalafil dose (or its matching placebo equivalent), then they are to stay on the 20 mg tadalafil daily dose (or its placebo equivalent) for the remainder of the double blind treatment period. These participants will receive the same treatment they received during their double blind titration phase Week 1 throughout the entire double blind treatment period.

** At the beginning of the open label treatment period, participants who were randomized to macitentan 10 mg only, or who could not tolerate 40 mg tadalafil, will receive an LC of 10 mg macitentan and 20 mg tadalafil for one week. Participants who were randomized to FDC or tadalafil 40 mg only and completed 16 weeks of double blind treatment with 40 mg tadalafil will receive an LC of 10 mg macitentan and 40 mg tadalafil during the first week of open label treatment. During the second week of open label treatment, all participants will receive an LC of 10 mg macitentan and 40 mg tadalafil. Treatment during the open label titration phase will be assigned by the IRT. Following the titration phase, all participants receive M/T FDC. Participants who cannot tolerate 40 mg tadalafil will be required to prematurely discontinue study treatment.

*** Participants who have discontinued double blind study treatment prematurely, will continue participation until Week 120 but will not receive open label treatment. Participants who have completed the 24 months of the open label period and are benefiting from the study intervention, as determined by their investigator, will be able to continue participation in the open label period beyond 24 months until alternative continued access is available in the patients country and as per local regulations via an open label extension study or via post study independent requests from their investigators if tadalafil 40 mg and macitentan 10 mg are not accessible for PAH in the patient's country.

**** For participants who completed the 24 months of open label treatment and who are eligible for a continued access program (post trial access program or other open label extension study) the S FU period will be waived. For these participants the EOS visit is defined as the EOLT and which should occur only if immediate transition, ie, on the same day as EOS into the continues access program is ensured.

3.1.1.1 Stratified randomization summary

Participants on ERA therapy at baseline are randomized 2:1 to M/T FDC or macitentan 10 mg, respectively.

Participants on PDE-5i therapy at baseline are randomized 2:1 to M/T FDC or tadalafil 40 mg, respectively.

Treatment-naïve participants at baseline are randomized 2:1:1 to M/T FDC, macitentan 10 mg, or tadalafil 40 mg, respectively.

3.1.1.2 Premature study treatment discontinuation

If a participant prematurely discontinues study treatment:

- Prior to prematurely discontinuing study treatment, participants should contact the site and schedule an EOT visit.
- If study treatment is prematurely discontinued during the double-blind treatment period, an EDBT visit is to be conducted within ±2 days of last study treatment intake, before initiation of any new PAH-specific therapy, and, if not possible, within 7 days after last study treatment intake. The participant will be asked to return for a safety follow-up visit 30 35 days after last study treatment intake and all other visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, M/M, AE, and concomitant medication information will be collected.
- If study treatment is prematurely discontinued during the open-label treatment period, an EOLT visit is to be conducted within 7 days of last study treatment intake. The participant will be asked to return for a safety follow-up visit 30 35 days after last study treatment intake, and all other visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, M/M, AE, and concomitant medication information will be collected.

- Survival status follow-up will be collected for all participants starting at the time of double-blind database lock and yearly thereafter until death or study closure [Section 8.2]. Refer to Section 7.2.2.13 for more details.

3.1.2 Study duration

The study starts with the first act of recruitment (ie, signature of the first ICF) and ends with the last visit of the last participant. It is estimated to last approximately 54 months.

The total study duration for a participant will be up to 30 months.

The study will continue at each site until all participants have completed the study or the sponsor decides to end the study.

3.2 Study Design Rationale

This is a prospective, multi-center, double-blind, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive Phase 3 clinical study with a double-blind treatment period duration of 16 weeks, followed by an open-label treatment period of up to 24 months.

A double-blind, randomized trial provides the most definitive and rigorous method of evaluating the efficacy of a medical treatment. The use of active comparators is essential to the trial's objective of evaluating the effect of the FDC vs the individual monotherapies.

The double-blind treatment period is planned for 16 weeks, as a study duration of 16 weeks has been demonstrated to be sufficient to observe improvement in hemodynamics as measured by RHC in studies of ERAs and PDE-5is individually [Ghofrani 2017, Galiè 2009]. Previous studies of PAH therapies have shown an average improvement in PVR of ~25%, which is considered to be clinically relevant [Krause 2018, Ghofrani 2017, Galiè 2009]. A decrease of PVR on PAH therapies has been associated with improvement in clinical outcomes [Gerges 2016, Tiede 2013, Nickel 2012]. The primary endpoint will be assessed at end of double-blind treatment, either at completion of 16 weeks or at time of premature discontinuation, to ensure an on-treatment measurement.

The tadalafil dose will be up-titrated over the first 2 weeks after randomization to align with current clinical practice.

One IA is planned when approximately 100 participants have completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment and after the global amendment 5 has been approved in all the countries. The purpose of this IA is to stop early for efficacy, to avoid exposing too many participants to monotherapy, if the FDC is shown to be the best treatment option, and to allow earlier access to a formulation that may help to improve compliance; to reassess the sample size based on conditional power and adapt if the initial assumptions are different than those observed; or to stop for futility in the case of low probability of success.

Participants who complete 16 weeks of double-blind treatment are eligible to continue into an open-label treatment period, during which all participants will be treated with M/T FDC. An open-label treatment period allows for the collection of long-term safety and tolerability information on the M/T FDC for participants who have already participated in the double-blind treatment period. Such designs are widely used in clinical programs to collect long-term safety data beyond completion of the original study.

- Regardless of length of study treatment, all participants will be followed until Week 120 and M/M data collected. Survival status follow-up will be collected for all participants starting at the time of double-blind database lock and yearly thereafter until death or study closure [Section 8.2]. Refer to Section 7.2.2.13 for more details.

3.3 Site Personnel and Roles

3.3.1 Right heart catheterization

Detailed guidance on the conduct of RHCs is provided in Section 14.1. Site team members conducting the RHCs must be instructed on these RHC guidelines. A training log must be collected upon completion of the training.

The RHC laboratory should be equipped to do thermodilution and/or indirect (assumed) Fick cardiac outputs, and should have the ability to record and print out all pressure tracings with clear scales and concurrent ECG tracings, as well as thermodilution curves and a standard log (printed electronic or hand-written paper log) of the procedure that includes the times and the measured vital signs during the procedure as is standard practice for any RHC laboratory. Use of the provided RHC worksheet is mandatory.

3.3.2 6-minute walk test

Site team members conducting the 6-minute walk test (6MWT) must be instructed on the sponsor's 6MWT guidelines [Section 14.2], and a training log must be collected upon completion of the training. Use of the provided 6MWT worksheet is mandatory.

3.4 Study Committees

A Steering Committee has been appointed by the sponsor to oversee the conduct of the study. The committee is governed by a dedicated Steering Committee charter.

An Independent Data Monitoring Committee (IDMC) has overall responsibility for safeguarding the interests of participants by monitoring unblinded safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC will interpret the results of the planned IA performed by the independent statistical support group (SSG), as outlined in Section 10.4. The IDMC and independent SSG will be fully operational prior to enrollment of the first participant into the study. The composition and operation of the IDMC is described in the IDMC charter.

An independent Clinical Events Committee (CEC) of PAH experts will review and confirm all reported mortality and morbidity events, including start date of the event, in a blinded fashion.

An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) has been appointed to monitor all studies with macitentan, and to provide ongoing assessment and advice regarding serious hepatic adverse events (AEs) of special interest that require further evaluation during the study.

4 SUBJECT POPULATION

4.1 Subject Population Description

This study will enroll male and female participants ≥18 years of age with RHC confirmed diagnosis of PAH (WHO Group 1). The study will include approximately 50% participants who are PAH-specific treatment-naïve.

Participants must be in WHO FC II or III and be eligible for dual therapy with an ERA and a PDE-5i. Participants with concomitant significant pulmonary or cardiac conditions other than PAH are not eligible to enter the study.

Eligible participants must be able and willing to give informed consent to participate in the clinical study.

4.2 Rationale for the Selection of the Study Population

Inclusion/exclusion criteria are selected to define a participant population with WHO Group 1 pulmonary hypertension (ie, PAH), the labeled indication for macitentan and tadalafil. Furthermore, inclusion/exclusion criteria were written in accordance with the labeled contraindications, precautions, and warnings for macitentan and tadalafil.

The minimum 6MWD is 100 m in order to avoid the imputation of missing values in participants who can hardly walk or cannot walk at all.

Exclusion of the remaining concomitant diseases and therapies listed below is based on the prescribing information or other background information for one or more of the study treatments [Macitentan/tadalafil FDC IB].

4.3 Inclusion Criteria

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

1. Signed and dated ICF.
2. Male and female participants ≥18 years old.
3. Confirmed diagnosis of symptomatic PAH in WHO FC II or III.
4. Symptomatic PAH belonging to one of the following subgroups of WHO Group 1 pulmonary hypertension [Simonneau 2013]:
    - Idiopathic.
    - Heritable.
    - Drug- or toxin-induced.
    - Associated with one of the following:
    - Connective tissue disease.
    - HIV infection.
    - Portal hypertension.
    - Congenital heart disease with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus) with persistent pulmonary hypertension documented by an RHC ≥1 year after surgical repair.
5. PAH diagnosis confirmed by hemodynamic evaluation at rest (through central reading), evaluated within 5 weeks prior to randomization.
    - Mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, AND
    - Pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) ≤15 mmHg, AND
    - Pulmonary vascular resistance (PVR) ≥ 3 WU (ie, ≥240 dyn·sec·cm $^{-5}$).
6. Negative vasoreactivity test in idiopathic, heritable, and drug/toxin-induced PAH. (Patients for whom no vasoreactivity test was performed at diagnosis can be eligible if currently treated

with PAH therapy for more than 3 months and PAH diagnosis confirmed by hemodynamic evaluation at least 3 months after introduction of their PAH therapy).

7. Criterion modified per Amendment 5

7.1 Currently receiving a stable dose of ERA or PDE-5i monotherapy for at least 3 months prior to baseline RHC, within the prespecified doses below or no history of PAH-specific treatment[6]:

- Bosentan: 250 mg total daily dose
- Macitentan: 10 mg total daily dose
- Ambrisentan: 10 mg total daily dose
- Sildenafil: 60 120 mg total daily dose
- Tadalafil: 40 mg total daily dose
- Vardenafil: 10 mg total daily dose

8. Participant able to perform the 6MWT with a minimum distance of 100 m and maximum distance of 450 m at Screening.
9. A woman of childbearing potential is eligible only if the following applies:
    - Negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization.
    - Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation.
    - Agreement to follow the contraception scheme from Screening up to at least 30 days after study treatment discontinuation.

4.4 Exclusion Criteria

Participants must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any participant.

PAH treatments:

1. Treatment with a soluble guanylate cyclase stimulator, L-arginine, any form of prostanoids or prostacyclin-receptor agonists (including oral, inhaled, or infused routes) in the 3-month period prior to start of treatment.
2. Treatment with combination therapy of ERA and PDE-5i in the 3-month period prior to start of treatment or history of intolerance to ERA and PDE-5i combination therapy.
3. Hypersensitivity to any of the study treatments or any excipient of their formulations.

Other therapies:

4. Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer (eg, rifabutin, rifampin, rifampicin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's Wort) in the 1month period prior to start of treatment.
5. Criterion modified per Amendment 3
   Treatment with a strong CYP3A4 inhibitor (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

[6] PAH specific treatment is defined as prostanoids, prostacyclin receptor agonists, guanylate cyclase stimulators, ERAs, or PDE 5is prescribed to treat PAH.

combination of moderate CYP3A4 and moderate CYP2C9 inhibitors in the 1-month period prior to start of treatment.
6. Treatment with doxazosin.
7. Treatment with any form of organic nitrate, either regularly or intermittently
8. Diuretic treatment initiated or dose changed within 1 week prior to the RHC or start of treatment.
9. Treatment with another investigational drug in the 3-month period prior to start of treatment.

Medical history/current medical conditions:
10. Body mass index (BMI) >40 kg/m^2 at Screening.
11. Known presence of 3 or more of the following risk factors for heart failure with preserved ejection fraction at Screening:
    - BMI >30 kg/m^2.
    - Diabetes mellitus of any type.
    - Essential hypertension (even if well controlled).
    - Coronary artery disease, ie, any of the following:
    - History of stable angina, or
    - Known more than 50% stenosis in a coronary artery, or
    - History of myocardial infarction, or
    - History of or planned coronary artery bypass grafting and/or coronary artery stenting.
12. Known presence of moderate or severe obstructive lung disease (forced expiratory volume in 1 second [FEV_1] / forced vital capacity [FVC] <70%; and FEV_1 <65% of predicted after bronchodilator administration) any time prior to Screening.
13. Known presence of moderate or severe restrictive lung disease (total lung capacity or FVC <60% of normal predicted value) any time prior to Screening.
14. Clinically significant aortic or mitral valve disease; pericardial constriction; restrictive or congestive leftsided cardiomyopathy; life-threatening cardiac arrhythmias; significant left ventricular dysfunction; or left ventricular outflow obstruction, in the opinion of the investigator
15. Known permanent atrial fibrillation, in the opinion of the investigator.
16. Known or suspected uncontrolled thyroid disease (hypo- or hyperthyroidism).
17. Documented pulmonary veno-occlusive disease.

Criteria linked to macitentan/tadalafil use:
18. Hemoglobin <100 g/L (<10 g/dL) at Screening.
19. Known severe hepatic impairment defined as a Model for End-Stage Liver Disease (MELD) score ≥19.[7]
20. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN) at Screening.
21. Criterion modified per Amendment 5

[7] See Section 14.8 for MELD scoring criteria.

21.1 Severe renal impairment (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation [Levey 2009] calculated creatinine clearance <30 mL/min) at Screening.[8]

22. Systemic hypotension (systolic blood pressure [SBP] <90 or diastolic blood pressure [DBP] <50 mmHg) at Screening or Randomization.
23. Systemic hypertension (SBP >160 or DBP >100 mmHg) at Screening.
24. Acute myocardial infarction or cerebrovascular event (eg, stroke) within the last 26 weeks prior to Screening.
25. Known bleeding disorder in the opinion of the investigator.
26. Loss of vision in one or both eyes because of non-arteritic anterior ischemic optic neuropathy, regardless of whether or not this episode was in connection with previous PDE-5i treatment.
27. Hereditary degenerative retinal disorders, including retinitis pigmentosa.
28. History of priapism, conditions that predispose to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia) or anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie's disease).

General restrictions:

29. Difficulty swallowing large pills/tablets that would interfere with the ability to comply with study treatment regimen.
30. Any planned surgical intervention (including organ transplant) during the double-blind treatment period, except minor interventions.
31. Exercise training program for cardiopulmonary rehabilitation in the 12-week period prior to Start of treatment, or planned to be started during the double-blind period of the study.
32. Pregnant, planning to become pregnant or lactating.
33. Any known factor or disease that might interfere with treatment adherence, study assessments, study conduct, or interpretation of the results as judged by the investigator (eg, drug or alcohol dependence, psychiatric disease, use of walking aids, etc.).
34. Known concomitant life-threatening disease with a life expectancy <12 months.

Other therapies:

35. Criterion added per Amendment 5

    Calcium channel blocker treatment initiated, or dose changed within 3 months prior to RHC at screening.

4.5 Criteria for Women of Childbearing Potential

4.5.1 Definition of childbearing potential

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

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy, or hysterectomy,

[8] Calculated creatinine clearance is measured as eGFR in this study (Section 7.2.4.2)

- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]),
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, or uterine agenesis.

The reason for not being of childbearing potential will be recorded in the electronic Case Report Form (eCRF).

4.5.2 Acceptable methods of contraception

Women of childbearing potential must use one of the following methods of contraception from Screening up to at least 30 days after study treatment discontinuation [Table 1].

Table 1 Acceptable methods of contraception

Option 1	**OR**	**Option 2**	**OR**	**Option 3**	**OR**	**Option 4**
		One method from this list				
• Tubal sterilization (occlusion or ligation of tubes at least 6 weeks prior to Screening) • Intrauterine devices • Implantable* hormonal contraceptives		• 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		**PLUS one method from this list**		
		• Diaphragm, • female condom • cervical cap, • partner's use of a condom		• Oral*, • Implantable*, • Transdermal*, or • Injectable* hormonal contraceptives • Intrauterine devices • Diaphragm, • female condom • cervical cap, • partner's use of a condom		

* If a hormonal contraceptive is chosen from this group, it must be taken for at least 28 days prior to Randomization.

Rhythm methods or the partner's use of a condom alone are not considered acceptable methods of contraception for this study.

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

To ensure compliance, the study personnel must remind women of childbearing potential at each visit to use the methods of contraception defined for this study. The reminders must be documented in the source documents.

5 TREATMENTS

5.1 Study Treatment

5.1.1 Investigational treatment: description and rationale

Study treatments are M/T FDC, macitentan, tadalafil, and their respective matching placebos. Details and references are provided in Section 1.2.

5.1.1.1 M/T FDC

M/T FDC will be provided as film-coated tablets.

The doses of macitentan (10 mg) and tadalafil (40 mg) selected for the M/T FDC are those recommended for each compound and correspond to the doses used for monotherapy.

The matching placebo tablets will not contain any active substance but are otherwise identical in appearance to the active drug tablets.

5.1.2 Comparator treatments: description and rationale

5.1.2.1 Macitentan 10 mg

Macitentan 10 mg will be provided as film-coated tablets debossed with ‘10’ on both sides.

The macitentan dose (10 mg) is the recommended dose and corresponds to the dose used, both separately and concomitantly, in the clinical setting.

The matching placebo tablets do not contain any active substance but are otherwise identical in appearance to the trial product.

5.1.2.2 Tadalafil 20 mg

Tadalafil 20 mg will be provided as over-encapsulated film-coated tablets.

The dose of tadalafil (40 mg) is the recommended dose and corresponds to the dose used, both separately and concomitantly, in the clinical setting.

The matching placebo tablets do not contain any active substance but are otherwise identical in appearance to the trial product.

5.1.3 Study treatment administration

5.1.3.1 Double-blind treatment period

Study treatment is to be taken from the day of the Randomization visit (Day 1). Tablets are to be taken at the same time each day, preferably in the morning, including on days of study visits.

Table 2 summarizes the different treatment administrations during the double-blind treatment period for each study treatment group.

Table 2 Treatment administration in the double-blind treatment period

Randomization	**M/T FDC[1]**	**Macitentan monotherapy[1]**	**Tadalafil monotherapy[1]**
Titration phase Week 1[2]	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 1 Tadalafil placebo tablet × 1	Macitentan 10 mg tablet × 1 Tadalafil placebo tablet × 2	Macitentan placebo tablet × 1 Tadalafil 20 mg tablet × 1 Tadalafil placebo tablet × 1
Titration phase Week 2[3]	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2	Macitentan 10 mg tablet × 1 Tadalafil placebo tablet × 2	Macitentan placebo tablet × 1 Tadalafil 20 mg tablet × 2
Maintenance phase[2]	Macitentan placebo tablet × 1 Tadalafil placebo tablet × 2 M/T FDC tablet × 1	Macitentan 10 mg tablet × 1 Tadalafil placebo tablet × 2 M/T FDC placebo tablet × 1	Macitentan placebo tablet × 1 Tadalafil 20 mg tablet × 2 M/T FDC placebo tablet × 1

M/T FDC macitentan/tadalafil fixed dose combination; PDE 5i phosphodiesterase type 5 inhibitor.

[1] Table lists tablets to be taken per day. All tablets are to be taken together daily. Tablets are to be taken at the same time of day each day, preferably in the morning, including days of study visits.

[2] Participants who were on an allowable dose of PDE 5i at baseline (40 mg tadalafil, 60 120 mg sildenafil, or 10 mg vardenafil daily) will not up titrate and will receive 40 mg tadalafil starting on study Day 1.

[3]. If a participant cannot tolerate the higher tadalafil dose (or placebo) during the titration period, the dose will be decreased back to 20 mg daily. Within the first 2 3 weeks after decreasing the dose (up to and including Week 4 / Visit 5) and with the investigator's approval, the participant is allowed to be re uptitrated to the tadalafil 40 mg daily dose (or its matching placebo equivalent). If the participant cannot tolerate the 40 mg dose again on the 2nd attempt to up titrate the tadalafil dose (or its matching placebo equivalent), then they are to stay on the 20 mg tadalafil daily dose (or its placebo equivalent) for the remainder of the double blind treatment period. These participants will receive the same treatment they received during their titration phase Week 1 throughout the entire double blind treatment period.

5.1.3.2 Open-label treatment period

All participants will receive M/T FDC.

In order to maintain the blind as participants enter the open-label treatment period, all participants will complete a 2-week titration phase, during which macitentan and tadalafil will be administered as a loose combination. Treatment during this titration period will be assigned by the Interactive Response Technology (IRT) system. Participants who completed 16 weeks of treatment with 40 mg tadalafil during the double-blind treatment period will not be up-titrated but will receive macitentan 10 mg and tadalafil 40 mg directly from Week 1.

The first dose of open-label treatment will be taken after all Week 16 assessments are complete, including RHC, either in the evening after the visit or the following day, depending on the participant's normal dosing schedule. On the following days, tablets are to be taken at the same time of day each day, preferably in the morning, including on days of study visits.

Table 3 summarizes the different treatment administrations during the open-label treatment period for each study treatment group.

Table 3 Treatment administration in the open-label treatment period

Randomization	**M/T FDC[1]**	**Macitentan monotherapy[1]**	**Tadalafil monotherapy[1]**
Titration phase Week 1[2]	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 1 Tadalafil placebo tablet × 1	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2
Titration phase Week 2[3]	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2	Macitentan 10 mg tablet × 1 Tadalafil 20 mg tablet × 2
Maintenance phase	M/T FDC tablet × 1	M/T FDC tablet × 1	M/T FDC tablet × 1

M/T FDC macitentan/tadalafil fixed dose combination.

[1] Table lists tablets to be taken per day. Tablets are to be taken at the same time of day each day, preferably in the morning each day, including days of study visits.

[2] Participants who received M/T FDC or tadalafil monotherapy and who completed 16 weeks of treatment with 40 mg tadalafil during the double blind treatment period will receive tadalafil 40 mg (tadalafil 20 mg tablet × 2) during Week 1. Participants allocated to these arms who could not tolerate 40 mg tadalafil during the double blind treatment period will up titrate from 20 mg to 40 mg during the first 2 weeks of open label treatment. If they can tolerate 40 mg tadalafil, they will be able to proceed to the open label treatment period maintenance phase with the fixed dose combination. Treatment will be provided to all participants as a loose combination to preserve the blind from the double blind treatment period.

[3] Participants unable to tolerate 40 mg tadalafil during the titration period are ineligible to continue onto the maintenance period.

5.1.4 Treatment assignment

At Screening, participants will be assigned a study-specific participant number by the IRT system. This number is kept throughout the study and is the main participant identifier. Note: In case of re-screening, a new participant number will be assigned.

After having verified that the participant meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT system at Visit 2 to randomize the participant. The IRT assigns a randomization number to the participant and assigns the treatment kit number, which matches the treatment arm assigned by the randomization list to the randomization number.

The randomization list is generated by an independent Contract Research Organization (CRO).

Participants will be stratified based on their prior PAH therapy: Treatment-naïve, on ERA therapy, or on PDE-5i therapy.

The treatment-naïve participants will be randomized in a 2:1:1 ratio into M/T FDC, macitentan 10 mg, or tadalafil 40 mg daily, respectively. Participants on ERA therapy will be randomized in a 2:1 ratio to M/T FDC or macitentan 10 mg daily, respectively. Participants on PDE-5i will be randomized in a 2:1 ratio to M/T FDC or tadalafil 40 mg daily, respectively.

Participants will be assigned treatment for the open-label treatment period titration phase by the IRT system in order to maintain the blind from the double-blind study period.

Further details are provided in the IRT specification document and study-specific IRT user manual.

5.1.5 Blinding

The first 16 weeks of this study will be performed in a double-blind fashion. The investigator and study personnel, the participants, the Site Managers (SMs), sponsor personnel, and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until the final double-blind analysis, ie, until the last randomized participant has completed 16 weeks of double-blind treatment or prematurely discontinues from the study and the database is finalized, or until the study is stopped prematurely.

Treatment arm assignment in the double-blind treatment period will remain blinded when participants enter the open-label treatment period.

Study treatments and their matching placebos are indistinguishable. All treatment kits will be packaged in the same way.

Sponsor personnel responsible for clinical study supply distribution will need to be unblinded to ensure adequate supply of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file, and measures taken per sponsor's standard operating procedure to maintain blinding of the study team.

Until the time of sponsor unblinding, the randomization list is kept strictly confidential and accessible only to authorized persons who are not involved in the conduct of the study.

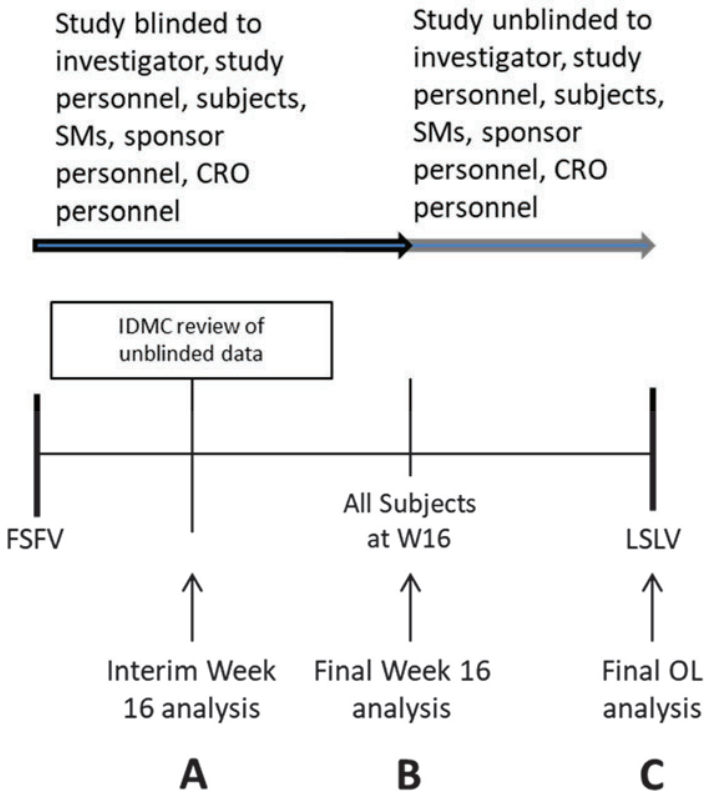
5.1.6 Unblinding

5.1.6.1 Timing of study analyses

The database will be cleaned and the data extracted and analyzed at 3 time points during the study [see Figure 2]:

1. The IA will take place when approximately 100 participants have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment and after the global amendment 5 has been approved in all the countries.
2. Unless the study is stopped prematurely during the IA, the final analysis of the double-blind period will occur when all participants have reached Week 16 or prematurely discontinued from the study.
3. The final analysis of the study will occur when all participants have performed their EOS visit (once the last participant has completed the open-label treatment period).

Figure 2 Study analyses



CRO Contract Research Organization; EOS End of Study; DB double blind; IDMC Independent Data Monitoring Committee; SM Site Manager; SSG statistical support group; FSFV First Subject First Visit; LSLV Last Subject Last Visit; M/T FDC macitentan / tadalafil FDC; OL open label; W week.

A Conducted by the independent SSG and interpreted by the IDMC when approximately 100 participants have either completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment and after the global amendment 5 has been approved in all the countries.
Analysis for efficacy or futility and sample size re estimation

B When all participants have reached Week 16 or prematurely discontinued from the study
Analysis of primary endpoint, secondary endpoints, and "other" endpoints for the double blind treatment period

C When all participants have performed their EOS visit
Final analysis of the study

5.1.6.2 Unblinding for IDMC

An independent SSG not otherwise involved in the design, conduct, or analysis of the study, will have access to the randomization code in order to prepare unblinded reports for review by the IDMC, as described in the IDMC charter. The independent SSG will be represented by an independent statistician. The randomization code will be made available to the independent SSG in accordance with the sponsor's Quality System (QS) documents.

5.1.6.2.1 Unblinding for the interim analysis

The independent SSG will have access to full randomization information for all participants randomized [see Section 5.1.6.2]. In accordance with the IDMC charter, the IDMC will review the study results [see Section 10.4] and will provide a recommendation on early study termination for efficacy or futility or on sample size adjustments.

If the study is terminated for efficacy, unblinding will occur after all enrolled participants have completed Week 16 assessments or prematurely discontinued the study.

5.1.6.3 Unblinding for the final double-blind treatment period analysis

Full randomization information will be made available to the sponsor for data analysis [see Figure 2] only after the last randomized participant has completed 16 weeks of double-blind treatment or has prematurely discontinued from the study, the database is cleaned, the data extraction is performed, in accordance with sponsor QS documents [see Figure 2].

Following each participant's completion of the double-blind treatment period, they will enter the open-label treatment period. In order to preserve the blind of each individual participant until the final double-blind analysis, all participants will enter a 2-week blinded titration period prior to initiating their M/T FDC treatment [see Section 5.1.3].

5.1.6.4 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a participant participating in the study, the sponsor will request the unblinding of the treatment assignment. The treatment assignment will not be communicated to site personnel or to the sponsor's CTT. Unblinded SUSAR information will be provided to respective health authorities and Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.5 Emergency procedure for unblinding

The investigator, study personnel, and sponsor personnel must remain blinded to the participant's treatment assignment. The identity of the study treatment may be revealed only if the participant

experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded treatment assignment through the IRT system. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible, and if it does not interfere with (or does not delay) any decision in the best interest of the participant, the investigator is invited to discuss the intended unblinding with sponsor personnel.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, sponsor personnel must be informed as soon as possible before or after the unblinding.

Unblinding must lead to study treatment discontinuation. Instructions for premature study treatment discontinuation are found in Section 5.1.10.

The circumstances leading to unblinding must be documented in the Investigator Site File (ISF) and eCRF.

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

Study treatment is provided as tablets and supplied in childproof blister packs during the double-blind treatment period and the titration phase of the open-label treatment period. Thereafter, during the open-label treatment period maintenance phase, study treatment is provided as tablets supplied in childproof bottles.

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

5.1.7.2 Study treatment distribution and storage

The investigator is responsible for the safe and proper handling and storage of the study treatments at the investigational site, and for ensuring that the study treatments are administered only to participants enrolled in the study and in accordance with the protocol. Study treatments must be kept in a locked cabinet or room, that can be accessed only by the pharmacist, the investigator, or another duly designated person.

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

At the site, a temperature log must be maintained, and temperature control should occur at least on a weekly basis.

5.1.7.3 Study treatment dispensing

The participants will receive sufficient study treatment to cover the period up to the next visit at which treatment dispensing is scheduled. Participants are asked to return all used, partially used, and unused study treatment blister packs/bottles at each visit. The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. The IRT system will allow dispensation of study treatment outside the scheduled visit. An accurate record of the date and amount of study treatment dispensed to each participant must be available for inspection at any time.

5.1.7.4 Study treatment return and destruction

Used and unused study treatment containers will be destroyed at the site once study treatment accountability is finalized and has been checked by sponsor personnel or the deputy, and written permission for destruction has been obtained from the sponsor, except in specific circumstances to be determined by the sponsor.

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

The inventory of study treatment dispensed to and returned by the participant (ie, study treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. It is to be recorded by site personnel on the study treatment dispensing and accountability log and in the eCRF and checked by the SM during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (ie, blister or bottle) dispensed to the participant:

- Allocated blister or bottle number (pre-populated in the eCRF).
- Dispensed blister or bottle number.
- Date dispensed / number of tablets dispensed.
- Date returned / number of tablets returned.

All study treatment supplies, including partially used or empty blisters or bottles must be retained at the site for review by the SM.

If the participant forgets to bring the remaining study treatment to a study visit, they must be instructed to not take any tablets from the remaining study treatment blisters or bottles and to return them at the next visit.

5.1.8.2 Study treatment compliance

Study treatment compliance must be evaluated by the SM. It is based on study treatment accountability. Compliance will be calculated separately for the 3 study treatments between 2 dispensing visits.

Compliance [(number of tablets dispensed number of tablets returned) / Total number of tablets that should have been taken during the period] × 100

The total number of tablets that should have been taken is calculated as follows:

	Titration phase		**Maintenance phase**
	Week 1	**Week 2**	
M/T FDC or placebo	Not applicable		Current visit date previous visit date
Tadalafil 20 mg* or placebo	2 × (Current visit date previous visit date)		
Macitentan 10 mg* or placebo	Current visit date previous visit date		

* Calculation of compliance for these tablets is not applicable during the open label treatment period maintenance phase.

Compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as protocol deviations, which will be reported in the mCTMS by the SM. The investigator must discuss the non-compliance with the participant to clarify the reasons and to take appropriate actions to avoid reoccurrence. This discussion and its outcome must be documented in the source documents.

5.1.9 Study treatment dose adjustments and interruptions

If a participant cannot tolerate 40 mg of tadalafil, the investigator may down-titrate the participant to 20 mg tadalafil.

If down-titration is determined to be necessary, an unscheduled visit is required, at which the investigator/delegate will contact the IRT system and new blister packs will be assigned in a blinded manner.

If down-titration occurs during the double-blind titration period, re-uptitration to 40 mg tadalafil may be attempted once during the first 2 weeks of the double-blind maintenance period. Re-uptitration may be performed at an unscheduled visit during the first 2 weeks of the double-blind maintenance period or at Visit 5. Re-uptitration can be done using originally assigned blister packs from the most recent study treatment dispensing visit.

Dose adjustments are not allowed for macitentan.

No dose adjustment is allowed during the open-label treatment period.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.11.

If study treatment is interrupted by the participant for any reason, they must immediately inform the investigator.

It is not allowed to interrupt only one of the study treatments (ie, tadalafil / macitentan / M/T FDC and/or matching placebos). All study treatments must be interrupted at the same time.

Interruptions of study treatment must be kept as short as possible. If treatment is stopped for more than 14 consecutive days, re-introduction is not permitted, and treatment must be permanently discontinued [see Section 5.1.10].

Study treatment dose adjustments / interruptions must be recorded in the eCRF.

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the participant, the investigator, or sponsor personnel. The main reason for and originator of the decision to prematurely discontinue study treatment must be documented in the eCRF.

It is not allowed to discontinue only one of the study treatments (ie, tadalafil / macitentan / M/T FDC and/or matching placebos). All study treatments must be discontinued at the same time.

A participant has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawal from study treatment only or by withdrawal from any further participation in the study (ie, premature withdrawal from the study [see Section 8.2]). Although a participant is not obliged to give their reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

The investigator must discontinue study treatment for a given participant if, on balance, they believe that continued administration would be contrary to the best interests of the participant.

Study-specific criteria for discontinuation of study treatment are described in Section 5.1.11.

A participant who prematurely discontinues study treatment is **NOT** considered withdrawn from the study.

If premature study treatment discontinuation occurs during the double-blind treatment period, the participant will be asked to return for a premature EDBT visit within ±2 days of last study treatment intake and before initiation of new PAH therapy (or, if not possible, within 7 days of the last intake of double-blind study treatment), a safety follow-up visit 30 35 days after the last intake of study treatment, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, M/M, AE, and concomitant medication information will be collected. Participants unable or unwilling to participate in these visits and/or phone calls should withdraw consent for the study. Participants that prematurely discontinue study treatment during the double-blind treatment period are not eligible to be treated with the M/T FDC during the open-label treatment period.

- Note: It is allowed to combine any of the above listed visits if their allowed visit windows overlap.

If premature study treatment discontinuation occurs during open-label treatment period, the participant will be asked to return for a premature EOLT visit within ±7 days of last intake of study treatment, safety follow-up visit 30 35 days after last intake of study treatment, and all remaining visits up until the Week 120 visit (excluding Visits 9 and 10). If the participant did not withdraw

consent for study participation and regular visits to the site are not possible, phone contacts can be performed, at the scheduled visits, until the Week 120 visit. During these phone calls, only M/M, AE, and concomitant medication information will be collected. Participants unable or unwilling to participate in these visits and/or phone calls should withdraw consent for the study.

- Note: it is allowed to combine any of the above listed visits if their allowed visit windows overlap.

A participant who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered withdrawn from the study. Participants who die or are lost to follow-up are also considered withdrawn from the study. Withdrawal from the study and follow-up medical care of participants withdrawn from the study, if applicable, are described in Sections 8.2 and 8.4, respectively. Survival status follow-up will be collected for all participants starting at the time of double-blind database lock and yearly thereafter until death or study closure [Section 8.2]. Refer to Section 7.2.2.13 for more details.

5.1.11 Study-specific criteria for interruption / premature discontinuation of study treatment

Study treatment interruptions exceeding 14 consecutive days must lead to permanent discontinuation of study treatments. If treatment interruption exceeds 14 consecutive days and thereby requires permanent discontinuation of study treatment, premature EOT visit should occur within 7 days of the discontinuation criteria being met. RHC is not required if it cannot be done within 7 days of last double-blind treatment administration.

5.1.11.1 Pregnancy

If a female participant becomes pregnant after study start (ie, signing of ICF) and up to 1 month following discontinuation of study treatment, a pregnancy form must be completed [see Section 9.3.1]. Therapy with all study treatments must be discontinued and the investigator should arrange for an appropriate standard-of-care approved PAH-specific therapy as needed.

5.1.11.2 Liver aminotransferases abnormalities

Interruption of study treatment
Study treatment must be interrupted in the following case:

- 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, reintroduction of study treatment can be considered.

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

Liver aminotransferase levels must be checked within 3 days after re-introduction, then again after a further 10 14 days and thereafter, if results remain within normal levels, per the normal assessment schedule described in Section 7.

Permanent discontinuation of study treatment
Study treatment must be stopped and its reintroduction is not to be considered in any of the following cases:

- Aminotransferase ≥8 × ULN.
- Aminotransferase ≥3 × ULN and associated clinical symptoms of liver injury, eg, nausea, vomiting, fever, abdominal pain, 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 treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Other diagnoses (eg, viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (eg, acetaminophen-related liver toxicity) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferase abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs [see Section 9.1].The ILSDRB provides ongoing assessment and advice regarding serious hepatic events that require further evaluation during the study.

5.1.11.3 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 (local) 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 values continue to remain >20 g/L below the baseline value at subsequent visits, further re-tests will be performed as per investigator's judgment.

Study treatment must be temporarily interrupted if clinically mandated based on the investigator's judgment, or in any of the following situations (unless clearly unrelated to study treatment, 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.

Reintroduction of study treatment may be considered if hemoglobin recovers, ie, if the hemoglobin value returns to above the lower limit of the normal range or to a value close to that at baseline, and if the potential benefits of reintroducing study treatment outweigh the potential risks.

5.1.11.4 Severe renal impairment

Study treatment must be discontinued in the event of severe renal impairment (estimated creatinine clearance <30 mL/min, CKD-EPI 2009 equation [Levey 2009]).

5.1.11.5 Vision disorder

Study treatment must be discontinued in case of loss of vision in one or both eyes.

5.1.11.6 Start of doxazosin and/or organic nitrates

Study treatment must be discontinued if doxazosin or any organic nitrate is started during treatment.

5.1.12 Study treatment overdose and treatment

For this study, any dose of study medication higher than the planned total daily dose in a single day will be considered an overdose.

In the event of an overdose, standard supportive measures must be taken, as required.

5.2 Previous and Concomitant Medications

5.2.1 Definitions

A previous medication is any treatment for which the end date is prior to the signing of the ICF.

A medication that is study-concomitant is any treatment that is ongoing or initiated after the signing of the ICF or initiated up to EOS.

A medication that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or initiated during the treatment period.

5.2.2 Reporting of previous/concomitant medications in the eCRF

The use of all study-concomitant medications (including contraceptives and traditional and alternative medicines, eg, plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous medications must be recorded in the eCRF if discontinued less than 30 days prior to the signing of the ICF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency, and indication will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

- Treatment with diuretics. Optimization of the dose of diuretics is allowed during the treatment period. Dose must be stable for at least 1 week prior to RHCs.
- Treatment with calcium channel blockers, if present at a stable dose for at least 3 months before RHC.

- During the 24 month open-label treatment period, addition of other PAH-specific therapy such as prostanoids or prostacyclin-receptor agonists (including oral, inhaled, or infused routes), soluble guanylate cyclase stimulators, or L-arginine is allowed after the first PAH worsening event as evaluated by the investigator.
- During the 24 month open-label treatment period, the patient may participate in pulmonary rehabilitation.

5.2.4 Forbidden concomitant therapy

During the 16-week double-blind treatment period:

- Treatment with any PAH therapy other than the study treatments, eg, other ERAs, other PDE-5is, prostanoids or prostacyclin-receptor agonists (including oral, inhaled, or infused routes), soluble guanylate cyclase stimulators, or L-arginine.
    - For participants on ERA or PDE-5i at baseline, the previous ERA or PDE-5i will be stopped on the day before the first administration of study treatment.

During open-label treatment period:

- Treatment with any ERA or PDE-5i other than the study drug.
- Treatment with prostanoids or prostacyclin-receptor agonists (including oral, inhaled, or infused routes), soluble guanylate cyclase stimulators, or L-arginine until the first suspected worsening event.

At any time during the study:

- Strong CYP3A4 inducers (eg, carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's Wort).
- Strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, and saquinavir).
- 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) until study intervention discontinuation, refer to Food and Drug Administration website [FDA 2020].
- Treatment with doxazosin.
- Any form of organic nitrate, either regularly or intermittently.
    - If treatment with organic nitrates (eg, nitroglycerin) is required for angina chest pain, at least 48 hours should elapse between the last dose of study medication and administration of nitrates. If nitrates are administered <48 hours after the last dose of study medication, close medical supervision with hemodynamic monitoring is strongly recommended.
- Any other investigational drug.

Study treatment must be interrupted if the participant requires treatment with a forbidden medication (see above). Study treatment may be restarted if the forbidden treatment is discontinued and study drug interruption does not exceed 14 days (see Section 5.1.11). Initiation of doxazosin or organic nitrates require (see Section 5.1.11.6) permanent study treatment discontinuation and the participant must complete an EOT visit.

Every effort should be made to complete EDBT efficacy assessments, most importantly RHC, within ±2 days of last study treatment intake and before initiation of any new PAH-specific therapy.

If patients enrolled in a prior version (protocol versions 1 through 3) of this protocol are currently stable on 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), the patient may remain on current treatment per the investigator's discretion based on his/her clinical judgement and risk-benefit assessment. However, the patient will not be eligible to enter the open-label treatment period unless the forbidden medication is discontinued 1-month prior to open-label treatment period.

6 STUDY ENDPOINTS

6.1 Efficacy Endpoints

All endpoints will be derived using values that have been collected while on double-blind treatment. The choice of an on-treatment is to reflect the treatment effect as any discontinuation of study treatment and/or introduction of another PAH medication is expected to have an immediate impact on hemodynamic characteristics. The definition of "on-treatment" values will be detailed in the estimand section of each endpoint.

The baseline value is the last valid assessment obtained prior to first dose of study treatment.

6.1.1 Primary efficacy endpoint

- Change in PVR expressed as the ratio of geometric means of EDBT to baseline.

Hemodynamic measures as outcomes in studies of PAH provide a robust and objective assessments of the status of the pulmonary circulation and are predictive of a participant's clinical outcome. RHC is the standard approach for the initial confirmation of the presence of pulmonary hypertension, for establishing the specific diagnosis (eg, PAH), determining the severity and prognosis of pulmonary hypertension, and for guiding therapy [Hoeper 2013, Galiè 2015a]. PVR (as measured by RHC) was chosen as the primary endpoint due to its association with disease severity and correlation with mortality [Benza 2012b, Fares 2016, Section 1.3]. In addition to its diagnostic [Hoeper 2013] and prognostic value, PVR as determined by RHC is needed to obtain an objective judgment on the hemodynamic response to treatment and to guide disease management [Tiede 2013, Galiè 2015a]. An increase in PVR worsens right ventricular afterload and thus leads to right ventricular overload, hypertrophy, dilatation, and eventually to right ventricular failure and death [Kholdani 2015, Vonk-Noordegraaf 2013, Ryan 2015, Galiè 2010].

Data from the SERAPHIN study support a correlation between changes in baseline PVR and clinical benefit. A statistically significant correlation (coefficient of correlation of 0.36 in 48 macitentan 10 mg patients and 50 placebo patients) was observed between percentage changes in PVR and percentage changes in 6MWD at Month 6. The effect change was consistent with the change in PVR defined as the log of the ratio of Month 6 to baseline PVR. Additional analyses were carried out to further characterize the log of the ratio of PVR as a potential "surrogate" for 2 clinical outcomes: absolute change from baseline to Month 6 in 6MWD and time to first M/M event up to EOT. The proportion of the treatment effect explained by the log (Month 6 PVR /

baseline PVR) was 66% for change in 6MWD and 40% for time to first M/M event in a Cox regression analysis (data on file).

6.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are listed here according to the hierarchical order that will be statistically tested:

- Change from baseline to EDBT in 6MWD.
  This endpoint reflects the participants' exercise capacity and has been associated with participants' prognosis / clinical outcomes including mortality [Benza 2012b, Benza 2015] and hemodynamics. It has also been the basis for registration of several of the currently approved PAH therapies.
- Change from baseline to Week 16 in PAH-Symptoms and Impact™ (PAH-SYMPACT™) in Cardiopulmonary symptom domain score
- Change from baseline to Week 16 in PAH-SYMPACTÔ in Cardiovascular symptom domain score
- Proportion of participants with absence of worsening in WHO FC from baseline to EDBT.

PAH-SYMPACT™ is a PAH-specific patient-reported outcomes instrument that quantifies PAH symptoms and impacts [McCollister 2016, Chin 2018].

WHO FC reflects the severity of a PAH patient's symptoms and the impact of these symptoms on their activities of daily life. WHO FC is directly associated with prognosis including mortality [Benza 2012b], and improvement in WHO FC correlates with survival in participants with PAH [Ghofrani 2016].

6.1.3 Other efficacy endpoints

6.1.3.1 Other efficacy endpoints for double-blind treatment period

Other efficacy endpoints for the double-blind treatment period are:

- Change from baseline to EDBT in PAH-SYMPACT™ Physical impact domain score.
- Change from baseline to EDBT in PAH-SYMPACT™ Cognitive/emotional impact domain score.
- Time to first morbidity or mortality event occurring between baseline and EDBT, defined as any of the following:
  - Death (all causes).
  - Non-planned PAH-related hospitalization.
  - Initiation of IV or subcutaneous prostacyclin or prostacyclin analog for worsening PAH.
  - Clinical worsening defined as:
  - Deterioration in exercise testing, confirmed by two 6MWTs performed on different days within 2 weeks, showing at least 15% decrease in 6MWD from baseline.

  AND
  - Worsening of PAH symptoms, defined as at least one of the following
    - Increase in WHO FC.

  - Appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

- Time to death due to PAH or hospitalization for PAH occurring between baseline and EDBT:
  - Death due to PAH, or onset of a treatment-emergent AE that led to permanent discontinuation of double-blind study treatment with a fatal outcome due to PAH occurring within 4 weeks of double-blind study treatment discontinuation.

  OR
  - Non-planned PAH-related hospitalization.
- Time to death (all causes) occurring between randomization and double-blind database lock.
- Change from baseline to EDBT in NT-proBNP.
- Change from baseline to EDBT in QoL, assessed by the Euro Quality of Life-5D-5L (EQ-5D-5L).
- Change from baseline to EDBT in work productivity and activity impairment, assessed by the Work Productivity and Activity Impairment Questionnaire©: General Health (WPAI©: GH).
- Changes from baseline to EDBT in the following hemodynamic variables:
  - Right atrial pressure.
  - Right ventricular stroke work index (RVSWI).
  - Right atrial pressure / PAWP ratio.
  - Stroke volume index (SVI).
  - Pulmonary artery pulsatility index.
  - Pulmonary artery compliance.
- Proportion of participants who achieve a right atrial pressure of $\leq$8 mmHg at EDBT.
- Number per year of all-cause and PAH-related hospitalizations, from baseline up to EDBT.
- Number per year of in-patient hospital days for all causes and PAH-related causes, from baseline up to EDBT.
- Number per year of emergency room visits for all causes and PAH-related causes that do not result in hospital admittance from baseline up to EDBT.

6.1.3.2 Other efficacy endpoints for open-label treatment period

Other efficacy endpoints for the open-label treatment period are:

- Change from baseline up to EOLT, by visit, in exercise capacity, as measured by the 6MWD.
- Change from baseline up to EOLT, by visit, in WHO FC.
- Time to first morbidity or mortality event occurring between baseline and EOLT, defined as any of the following:
  - Death (all causes).
  - Non-planned PAH-related hospitalization.
  - Initiation of IV or subcutaneous prostacyclin or prostacyclin analog for worsening PAH.
  - Clinical worsening defined as:
    - Deterioration in exercise testing, confirmed by two 6MWTs performed on different days within 2 weeks, showing at least 15% decrease of 6MWD from baseline.

  AND
    - Worsening of PAH symptoms, defined as at least one of the following
      - Increase in WHO FC.

  - Appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

- Time to death due to PAH or hospitalization for PAH occurring between baseline and EOLT:
  - Death due to PAH, or onset of a treatment-emergent AE that led to permanent discontinuation of study treatment with a fatal outcome due to PAH occurring within 4 weeks of study treatment discontinuation

  OR
  - Non-planned PAH-related hospitalization.
- Time to death (all causes) occurring between randomization and open-label database lock.
- Change from baseline up to EOLT, by visit, in NT-proBNP.
- Number per year of all-cause and PAH-related hospitalizations, from baseline up to EOLT.
- Number per year of in-patient hospital days for all causes and PAH-related causes, from baseline up to EOLT.
- Number per year of emergency room visits for all causes and PAH-related causes that do not result in hospital admittance from baseline up to EOLT.

6.2 Safety endpoints

For the safety endpoints, analysis will be done for each of the safety sets defined in [Section 10.1] The safety endpoints are:

- Treatment-emergent AEs.
- SAEs.
- Deaths.
- AEs leading to premature discontinuation of study treatment.
- Change in vital signs (SBP, DBP, and pulse rate) and body weight from baseline to all assessed time points during the study.
- Treatment-emergent marked laboratory abnormalities as detailed in Section 14.4.
- Proportion of participants with a treatment-emergent ALT and/or AST abnormality (≥3, ≥5, and ≥8 × ULN).
- Proportion of participants with a treatment-emergent ALT and/or AST abnormality (≥3 × ULN) associated with total bilirubin ≥2 × ULN (and increased as compared to baseline).
- Proportion of participants with a treatment-emergent hemoglobin abnormality (<100 g/L, and <80 g/L).
- Treatment-emergent AEs of special interest (hypotension, anemia, edema, liver events).

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 General Information

The study visits are listed in Table 4 and Table 5. For all visits, the participants must be seen on the designated day with an allowed visit window of 7 days, however all efforts must be made to have EDBT efficacy assessments completed within ±2 days of last study treatment intake and before initiation of any new PAH-specific therapy. A follow-up safety visit must be performed 30 35 days after intake of the last dose of study treatment. All assessments pertaining to a visit should be performed on the same day. If it is not possible to complete all assessments on the same day, a visit may extend over more than 1 day within the allowed time window.

Participants who prematurely discontinue study treatment for any reason will not be replaced.

7.1.1 Screening/re-screening

Screening starts with the signature of the ICF. The date on which the first screening assessment is performed corresponds to the date of the Screening visit.

It is the responsibility of the investigator/delegate to obtain written informed consent from each participant participating in this study after adequate face-to-face explanation of the objectives, methods, and potential hazards of the study. The participants who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

Participants who have signed the ICF and are in screening when the enrollment target has been met may still be randomized.

It is permitted to re-screen participants once, if the reason for non-eligibility was transient (eg, abnormal laboratory test, insufficient washout period of a forbidden medication). All screening assessments (except RHC if already done for initial screening and still within 5 weeks of randomization) should be repeated at the time of re-screening.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (eg, AE), appropriate assessments will be performed based on the judgment of the investigator, and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule as originally planned.

Table 4 Double-blind treatment period visit and assessment schedule

PERIODS	Name	Screening	Double-blind treatment period									
PHASES	Name		Titration			Maintenance						
VISITS	Number	1	2	3 ☎	4 ☎	5	6	7	8		*U1, U2, …*	*Survival F-U*
	Name	Screening	Start of treatment						EDBT[9,10]	Premature EDBT[9,10]	*Unscheduled visit*[1]	
	Time	Within 30 days of Day1	Day 1	Week 1/ Day 8 (± 3 days)	Week 2/ Day 15 (± 3 days)	Week 4/ Day 29 (± 7 days)	Week 8/ Day 57 (± 7 days)	Week 12/ Day 85 (± 7 days)	Week 16/ Day 113 (± 7 days)	At time of premature discontinuation (+2 days)	*Any time*	For all participants: Within 2 months prior to last participant's Week 16 visit (announced) and yearly thereafter until death or within 2 months prior to the last participants last visit (announced)[14]
Informed consent		X										
Demographics		X										
Medical history		X										
Right heart Catheterization		X†							X[11]	X[12]		
Concomitant therapy		X	X	X	X	X	X	X	X	X	*(X)*	
Physical examination[7]		X	X			X	X	X	X	X	*(X)*	
Vital signs		X	X			X	X	X	X	X	*(X)*	
Body weight, height[2]		X	X				X		X	X		
6MWT, Borg, WHO FC		X	X				X		X	X	*(X)*	
PAH-SYMPACT™**,[13]		X							X	X		
EQ-5D-5L / WPAI©,[13]			X						X	X		
PGA-S[13]			X						X	X		

PERIODS	Name	Screening	Double-blind treatment period									
PHASES	Name		Titration			Maintenance						
VISITS	Number	1	2	3 ☎	4 ☎	5	6	7	8		*U1, U2, …*	*Survival F-U*
	Name	Screening	Start of treatment						EDBT[9,10]	Premature EDBT[9,10]	*Unscheduled visit*[1]	
	Time	Within 30 days of Day1	Day 1	Week 1/ Day 8 (± 3 days)	Week 2/ Day 15 (± 3 days)	Week 4/ Day 29 (± 7 days)	Week 8/ Day 57 (± 7 days)	Week 12/ Day 85 (± 7 days)	Week 16/ Day 113 (± 7 days)	At time of premature discontinuation (+2 days)	*Any time*	For all participants: Within 2 months prior to last participant's Week 16 visit (announced) and yearly thereafter until death or within 2 months prior to the last participants last visit (announced)[14]
PGI-C[13]									X	X		
NT-proBNP*,[13]			X						X	X		
Biomarker sample[8,13]			X						X	X		
Laboratory tests*[3,13] / pregnancy[4] tests[4,13]		X	X			X	X	X	X	X	*(X)*	
Morbidity/mortality event assessment				X	X	X	X	X	X	X	*(X)*	
Study treatment dispensing/return[5]			X	*(X)*	*(X)*	X	X		X		*(X)*	
Adverse events[6]		X	X	X	X	X	X	X	X	X	*(X)*	
Serious adverse events[6]		X	X	X	X	X	X	X	X	X	*(X)*	
Survival F-U[14]												X

* Transferred electronically by an external service provider.

** The PAH SYMPACT questionnaire is filled out on an electronic device by the participant at home for 7 consecutive days prior to the applicable visit. Participants will be trained on how to use the PAH SYMPACT questionnaire during the Screening period. For the baseline questionnaire during the Screening period, the participant is given the questionnaire at the Screening visit and is to fill it out during 7 consecutive days in the Screening period. The baseline RHC is not to be done during the 7 consecutive days of the PAH SYMPACT.

†RHC conducted per guidelines in Section 14.1 done before Screening period is allowed provided it is done no more than 5 weeks prior to the date of randomization. Vasoreactivity test required for incidence patients. For prevalent patients without prior vasoreactivity test, they can be eligible if currently treated with PAH therapy for more than 3 months and PAH diagnosis confirmed by hemodynamic evaluation at least 3 months after introduction of their PAH therapy.

☎Visit may be conducted by phone.

X mandatory assessment; *(X)* Optional assessment.

[1] Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, including dispensing of down titration kits, based on the judgment of the investigator.

[2] Height is only measured at Visit 1.

[3] Includes hematology and blood chemistry.

[4] Serum pregnancy test at Screening only, urine pregnancy test for the following visits. Women of childbearing potential only.

[5] Scheduled study medication dispensing/return procedures may be adapted according to the site practice. Not applicable after premature study treatment discontinuation after last dispensed drug has been returned.

[6] All AEs and SAEs that occur after signing the ICF and up to EOS must be reported.

[7] The physical examination at Visit 1 and 2 must be performed in entirety for all participants but afterwards it must be tailored to organs that are prompted *ad hoc* by anamnesis.

[8] Biomarker samples collected for participants who agreed to biomarker sample collection in the ICF.

[9] EDBT efficacy assessments are to be conducted within 2 days after last study treatment intake and before introduction of any prohibited medications as listed in Section 5.2.4.

[10.] If participant does not enter open label treatment period, Safety Follow up visit is to be performed 30 35 days after last double blind study treatment intake [see Table 5]. Participants that prematurely discontinue study treatment during the double blind treatment period are not eligible to be treated during the open label treatment period.

[11.] RHC is to be performed at time of study treatment discontinuation. If RHC is performed at premature EDBT, then it is not to be performed at Week 16.

[12] If the study treatment is prematurely discontinued within 6 weeks after randomization, a post baseline RHC is not required.

[13] If study treatment is prematurely discontinued, these assessments are not required after the Safety Follow up visit.

[14.] Survival information will be collected for all participants (within 2 months prior to last participant's Week 16 visit [announced]). Thereafter survival status is collected approximately yearly until death or within 2 months prior to the last participants last visit (announced), including those who prematurely discontinued from the study at any time (Section 7.2.2.13 and Section 8.2).

6MWT 6 minute walk test; AE adverse event; EDBT End of Double Blind Treatment; EQ 5D 5L Euro Quality of Life 5D 5L; F U follow up; ICF Informed Consent Form; NT proBNP N terminal pro B type natriuretic peptide; RHC right heart catheterization; SAE serious adverse event; WHO FC World Health Organization functional class; WPAI© Work Productivity and Activity Impairment Questionnaire©.

Table 5 Open-label treatment period visit and assessment schedule

PERIODS	Name	Open-label treatment period									SAFETY FOLLOW-UP[6]	*Survival F-U*
PHASES	Name	Titration			Maintenance							
VISITS	Number	8	9	10	11	12	13	14		*U1, U2, …*	15	
	Name	EDBT	☎	☎				EOLT[11]	*Premature EOLT*	*Unscheduled visit*[1]	Safety Follow-up	
	Time	Week 16/ Day 113 (± 7 days)	Week 17/ Day 120 (± 3 days)	Week 18/ Day 127 (± 3 days)	Week 42/ Day 295 (± 7 days)	Week 68/ Day 477 (± 7 days)	Week 94/ Day 659 (± 7 days)	Week 120/ Day 841 (± 7 days) or premature discontinuation	*At time of premature discontinuation (± 7 days)*	*Any time*	30 35 days after last dose[6]	For all participants: Within 2 months prior to last participant's Week 16 visit (announced) and yearly thereafter until death or within 2 months prior to the last participants last visit (announced)[12]
Concomitant therapy		X	X	X	X	X	X	X	X	*(X)*	X	
Physical examination[5]		X			X	X	X	X	X	*(X)*		
Vital signs, body weight		X			X	X	X	X	X	*(X)*		
6MWT, Borg, WHO FC		X			X	X	X	X	X	*(X)*		
NT-proBNP*[,8]		X			X	X	X	X	X			
Biomarker sample[7,8]		X			X	X	X	X	X			
Laboratory tests*[,8, 10]		X[10]			X	X	X	X	X	*(X)*	X	
Liver function tests*[,8,9]		X			Monthly (± 7days)	Every 3 months (± 7days)			X		X	
Pregnancy tests[2,8]		← Monthly (± 7days) →							X		X	
Morbidity/mortality event assessment		X			X	X	X	X	X	*(X)*	X	
Study treatment dispensing/return[3]		X			X	X	X	X	X	*(X)*		
Semi-structured qualitative interview[13]					*(X)*							
Adverse events[4]		X	X	X	X	X	X	X	X	*(X)*	X	
Serious adverse events[4]		X	X	X	X	X	X	X	X	*(X)*	X	
Survival F-U[12]												X

* Transferred electronically by an external service provider.
☎Visit may be conducted by phone, not required if the participant has discontinued study treatment.
X mandatory assessment; *(X)* Optional assessment.

1 Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments based on the judgment of the investigator.
2 Urine pregnancy tests may be performed by women of childbearing potential at home and the results relayed to the site via phone call.
3 Scheduled study medication dispensing/return procedures may be adapted according to the site practice. Not applicable after premature study treatment discontinuation after last dispensed drug has been returned.
4 All AEs and SAEs that occur after signing the ICF and up to EOS must be reported.
5. The physical examination may be tailored to organs that are prompted *ad hoc* by anamnesis.
6 Safety Follow up visit happens after last dose of study treatment, this may be after the double blind treatment period or the open label treatment period. The S FU period will be waived for participants who completed the 24 months of open label treatment and who are eligible for continued access program (post trial access program or other open label extension study). For these participants the EOS visit is defined as the EOLT and which should occur only if immediate transition into the continues access program is ensured, ie, on the same day as EOS.
7. Biomarker samples collected for participants who agreed to biomarker sample collection in ICF.
8 If study treatment is prematurely discontinued, these assessments are not required after the Safety Follow up visit
9 During the open label treatment period, liver function tests are to be done monthly up until Week 42, and at least every 3 months thereafter up until the EOLT. Monthly liver tests are recommended during the entirety of the open label treatment period
10 Includes hematology laboratory test at Weeks 20, 24, and 36.
11. Participants who have completed 24 months of the open label period and are benefiting from the study intervention, as determined by their investigator, will be able to continue participation in the open label period until alternative continued access is available in the patient's country and as per local regulations via an open label extension study or via post study independent requests from their investigators if tadalafil 40 mg and macitentan 10 mg are not accessible for PAH in the patient's country.
12 Survival information will be collected for all participants (within 2 months prior to last participant's Week 16 visit [announced]). Thereafter survival status is collected approximately yearly until death or within 2 months prior to the last participants last visit (announced), including those who prematurely discontinued from the study at any time (Section 7.2.2.13 and Section 8.2).
13 Qualitative interviews will be conducted by an external vendor during the maintenance phase of the OL treatment period in participants that provided consent, as well as a subset of investigators as soon as amendment version 6 has been approved at the respective study site.

6MWT 6 minute walk test; AE adverse event; eCRF electronic Case Report Form; EDBT End of Double blind Treatment; EOLT End of Open Label Treatment; EOS End of Study; F U follow up; ICF Informed Consent Form; NT proBNP N terminal pro B type natriuretic peptide; SAE serious adverse event; WHO FC World Health Organization functional class.

7.2 Study Assessments

The study assessments are listed in Table 4 and Table 5. The assessments that are mandatory during a visit are marked with an 'X'. Optional assessments are marked with an '(*X*)'.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel, as required) and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

At Screening, the RHC (which is the most invasive study-specific procedure) should be performed after all other assessments are done and the participant has met all inclusion criteria and none of the exclusion criteria up to that point.

At all visits, the following order of assessments is recommended:

- PAH-SYMPACT™ completed at participant's home, 7 consecutive days prior to visit (when applicable).
- PGA-S, PGI-C, EQ-5D-5L and WPAI©: GH questionnaires (when applicable).
- Vital signs and physical exam.
- WHO FC evaluation (when applicable).
- 6MWT (when applicable).
- Blood samples for complete laboratory tests including hematology, blood chemistry, serum pregnancy test (for females of childbearing potential only), and biomarkers.
- RHC at rest (when applicable).

If the Principal Investigator (PI) delegates any study procedure/assessment for a participant to an external facility, they should inform the sponsor to whom these tasks are delegated. The set-up and oversight will be agreed upon with the sponsor. The supervision of any external facilities remains the responsibility of the PI.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the screening of the first participant:

- Temperature measurement devices for study treatment storage area.
- Temperature measurement devices for freezer storage of biomarker samples.
- Evidence of maintenance of the RHC equipment.

Calibration certificates of other equipment must be available per local requirements.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristics data to be collected on all randomized participants include: age, sex, race, ethnicity, and the reason why a female is considered not to be of childbearing potential. They are recorded in the eCRF at Visit 1 / Screening. 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 signature of the ICF will be recorded on the medical history page. Where possible, diagnoses and not symptoms will be recorded.

The Screening RHC should be done only after all other inclusion/exclusion criteria have been met.

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

- Date of screening.
- Reason for screening failure.
- All baseline data collected until confirmation of the screening failure.

7.2.2 Efficacy assessments

For the primary and secondary efficacy endpoints, the baseline value is the last valid assessment obtained prior to Randomization.

7.2.2.1 Right heart catheterization

For the RHC methodology to be used, see the sponsor guidelines for the RHC procedure [Section 14.1].

Results and other corresponding RHC documents must be kept as source data in the participant's file at the site.

The RHC laboratory should be equipped to do thermodilution and/or indirect (assumed) Fick cardiac outputs and should have the ability to record and print out all pressure tracings with clear scales and concurrent ECG tracings, as well as thermodilution curves.

Inclusion will be based on central reader evaluation of RHC data collected within 5 weeks prior to Randomization.

Completion of baseline and follow-up RHC will be confirmed by the site staff in the eCRF and the raw data (traces) will be made available to the central reading facility. The site will enter the following variables into the eCRF at baseline and EDBT:

- Date and time of the RHC.
- Date and time of last dose of study treatment intake prior to RHC.
- Heart rate during RHC.
- Systolic systemic artery pressure (Noninvasively measured).
- Diastolic systemic artery pressure (Noninvasively measured).
- Mean right atrial pressure (mRAP).
- Systolic pulmonary artery pressure.
- Diastolic pulmonary artery pressure.
- Pulmonary artery wedge pressure (PAWP).
- Left ventricular end diastolic pressure (LVEDP) (if available/measured).
- Pulmonary Vascular Resistance (PVR).
- Arterial oxygen saturation (non-invasively measured via an oximeter).
- Mixed venous oxygen saturation (blood sample taken from the distal port of the pulmonary artery catheter when the catheter is successfully placed in the pulmonary artery).
- Cardiac output (calculated by thermodilution and/or Fick).
- Hemoglobin value used to calculate Indirect Fick cardiac output.

The central reader evaluates the raw data in a blinded fashion and provides the following variables via central data transfer:

- Pulmonary Vascular Resistance (PVR)
- Mean right atrial pressure (mRAP).
- Systolic pulmonary artery pressure.
- Diastolic pulmonary artery pressure.
- Mean pulmonary artery pressure (mPAP).
- Pulmonary artery wedge pressure (PAWP).
- Left ventricular end diastolic pressure (LVEDP) (if available/measured).
- Cardiac output (calculated by thermodilution and/or Indirect Fick).

For all invasively measured pressures, the value should be entered as measured at end expiration, not as software-generated electronic average.

Other hemodynamic variables (including, cardiac index, RVSWI, etc.) will be calculated by the sponsor from the above measured hemodynamic variables [see Section 14.1].

If the primary investigational site does not have the possibility to perform an RHC, the sponsor could support the assessment at another investigational specialized site participating in this study (preferentially in the same country). The investigator at the primary site remains accountable for the review and submission of RHC data to the central reader.

Results of RHC are to be recorded on the provided sponsor Heart Catheterization Worksheet.

7.2.2.1.1 Baseline RHC

All participants must have an RHC performed per guidelines detailed in Section 14.1.

A historical RHC performed before ICF signature but within 5 weeks prior to Randomization (Visit 2) is allowed, provided conditions will be reproduced for the post-baseline RHC and meet the criteria detailed in the sponsor guidelines for RHC [Section 14.1].

7.2.2.1.2 EDBT RHC

EDBT RHC is an on-treatment assessment and is to be done no more than 2 days after last double-blind study treatment intake and before initiation of any new PAH-specific therapy. In the extraordinary case this is not possible, RHC can be performed up to 7 days after last double-blind study treatment intake. If RHC is performed more than ±2 days after the last day of double-blind study treatment intake or after initiation of new PAH-specific therapy, the results will not be used for the primary analysis on the primary endpoint; rather they will be used for a supportive analysis on the primary endpoint. If RHC cannot be performed within 7 days post last double-blind treatment administration, RHC procedure is not mandated for this study.

The EDBT RHC must be performed at the same location, under the same conditions (eg, same method, same flow of oxygen if applicable), and preferably by the same operator as the baseline RHC, and according to the guidelines detailed in Section 14.1.

7.2.2.2 6-minute walk test and Borg CR10 Scale®

See Table 4 and Table 5 for time points of assessment.

The 6-minute walk test (6MWT) is a non-encouraged test that measures, the distance walked in 6 minutes [Holland 2014]. The Borg CR10 Scale® measures a participant's dyspnea [Borg 1998].

Detailed guidelines on correct execution of these tests, the "Sponsor guidelines for the 6MWT", are provided in Section 14.2. The site team member conducting the 6MWT must be trained on these 6MWT guidelines. A training log must be collected upon completion of the training. Use of the provided 6MWT worksheet is mandatory.

Before study start, it must be verified (via the sponsor "6MWT Corridor Card") that the site can comply with these guidelines. The exact length of the corridor used at site should be documented on the site 6MWT Corridor Card. The same corridor should be used for all assessments.

It is important that, for each individual participant, the 6MWT is conducted under the same conditions throughout the study (eg, same corridor). In addition, if possible, for each individual participant, the 6MWT should be conducted by the same tester and preferably at the same time at each visit.

Note 1: If oxygen supplementation is needed during the 6MWT at Randomization then oxygen should be delivered using the same method, carrying the bottle in the same way, and using the same flow during all study 6MWTs by that participant. If the flow must be increased during subsequent visits (eg, due to worsening / increased oxygen requirements), this should be indicated in the source notes as well as in the concomitant medication forms of the eCRF.

Note 2: The oxygen flow rate (if applicable) must remain constant from 1 hour prior to each 6MWT until the completion of heart rate (HR) measurement 2 minutes after the end of the 6MWT.

Note 3: For consistency reasons, participants who were enrolled before the approval of Protocol AC-077A301 Amendment 2 Version 3 in their country must use the originally provided Borg Scale through the study.

Note 4: If the participant must wear a face mask during 6MWD assessment (eg, due to COVID-related safety measures), this must be documented in the source documents and in the eCRF.

The data related to 6MWT will be recorded in the eCRF and the provided sponsor 6MWT Worksheet.

7.2.2.3 PAH-SYMPACT questionnaire

The PAH SYMPACT™ questionnaire is a patient-reported outcome instrument that was developed by Actelion Pharmaceuticals Ltd for use in PAH patients [McCollister 2016; Chin 2018].

Participants will be trained on how to use the PAH SYMPACT™ questionnaire during the Screening period.

The PAH-SYMPACT™ will be administered during the Screening period and for the 7 consecutive days prior to the Week 16 visit (and premature EDBT visit for participants who prematurely discontinue during double-blind treatment).

The baseline PAH-SYMPACT™ is to be completed for 7 consecutive days during the Screening period. The baseline RHC should not be done during the 7 consecutive days of PAH-SYMPACT™. The EDBT PAH-SYMPACT™ is to be completed for the 7 consecutive days prior to the EDBT visit.

The PAH SYMPACT™ questionnaire is to be completed by the participant.

The PAH-SYMPACT™ will not be administered to illiterate participants, defined as participants who were unable to sign the ICF for themselves. It will also not be administered if the questionnaire is not available in a language that can be easily understood and read by the participant.

The PAH-SYMPACT™ should be completed in the evening, before bedtime.

The PAH-SYMPACT™ consists of 2 parts: Symptoms and Impacts.

The Symptom part is a daily diary that contains 11 items. The respondent is asked to rate each of the items for the past 24 hours. The response options for each item range from 0 "no [symptom] at all" to 4 "very severe". The symptom part is completed daily, as symptoms are experienced on a daily basis and severity may vary from one day to the next.

The Symptom part is completed for the 7 consecutive days (ie, starting 7 days prior to the visit day).

The Impact part has a 7-day recall period, as impacts of symptoms may not be experienced every day. It contains 11 items pertaining to the impact of the disease on the participant's life. The response options for each item range from 0 "yes, with no difficulty at all" to 4 "no, not able at all" / "yes, with extreme difficulty" / "extremely" / "very much". The Impact part is completed once on the 7th day of the symptoms diary data collection period, together with the Symptom part (ie, in the evening).

A sample of the PAH-SYMPACT™ questionnaire (US English) is provided as Section 14.5.

The PAH-SYMPACT™ will be administered on an electronic device. Participants will be trained on the completion of this questionnaire by the site staff during Visit 1 (Screening), prior to them completing the PAH-SYMPACT™ for the first time.

7.2.2.4 WHO FC

See Table 4 and Table 5 for time points of assessment.

When applicable, the WHO FC assessment should be performed before the 6MWT. The WHO FC will be collected in the eCRF.

WHO functional classification of pulmonary hypertension is found in Section 14.3.

7.2.2.5 Morbidity/Mortality event assessment

See Table 4 and Table 5 for time points of assessment.

Occurrence and date of M/M events will be collected in a separate eCRF page.

Morbidity/mortality events are also AEs/SAEs and must be assessed up to EOS.

Morbidity/mortality events, including start date of the event, will be adjudicated by an independent CEC in a blinded fashion to confirm they meet the definition of a M/M endpoint event as defined in Section 6.1.3. The CEC may request additional data from sites if it is needed for adjudication.

7.2.2.6 NT-proBNP

See Table 4 and Table 5 for time points of assessment.

A blood sample for analysis of NT-proBNP will be drawn at each applicable visit.

NT pro-BNP samples will be stored frozen (between 20 °C [4 °F] and 80 °C [112 °F], ±2 °C [±3.6 °F]).

A temperature log must be maintained and temperature control should occur at least on a weekly basis.

Further details regarding blood sampling procedures and the collection and shipment of biomarkers samples are described in the central laboratory manual.

7.2.2.7 Optional biomarker assessment

See Table 4 and Table 5 for time points of assessment.

When signing the ICF, participants are able to opt-in to optional blood collection for analysis of additional exploratory biomarkers related to pulmonary and cardiac function. Samples will be drawn using the central laboratory kit. Biomarkers tested will include, but are not limited to:

- sEndoglin.
- sFLT-1.
- VEGF-A.

Additional biomarkers may be included in the analysis if scientific rationale becomes available through research.

The biomarker analysis will be performed after study closure and will not be included in the study report.

Blood sampling procedures and the storage and shipment of the biomarker samples are described in the central laboratory manual. The biomarker samples will be transferred to a sponsor-designated biobank when the study is closed and may be stored there for a maximum of 15 years. Participants may request that these samples be destroyed at any time during or after the study.

7.2.2.8 EQ-5D-5L

The EQ-5D-5L will be administered at Randomization (Visit 2) and the Week 16 visit (Visit 8; and premature EDBT for participants who prematurely discontinue during double-blind treatment).

The EQ-5D-5L is to be completed by the participant and will be administered on an electronic device. It is recommended that the EQ-5D-5L be completed prior to any clinical assessments. Preferably, participants will complete the EQ-5D-5L while waiting for their appointment before any interaction with health care providers to avoid any potential bias in their responses.

The EQ-5D-5L will not be administered to illiterate participants, defined as participants who were unable to sign the ICF for themselves. It will also not be administered if the questionnaire is not available in a language that can be easily understood and read by the participant.

The EQ-5D-5L consists of a descriptive system (the questionnaire), and the EQ visual analog scale (VAS):

- The questionnaire assesses health status according to 5 dimensions (Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression). Each dimension is divided into 5 levels (I have no problem, I have slight problem, I have moderate problem, I have severe problem, I am unable to perform the described activity).
- The EQ VAS is a vertical scale, with endpoints of 100 (best imaginable state) at the top and 0 (worst imaginable state) at the bottom, which offers a simple method for obtaining a self-rating of current health-related QoL.

Only the version of the questionnaire and scale provided by the sponsor can be used. A sample of the EQ-5D-5L questionnaire (English version for the UK) and VAS is provided as Section 14.6.

Janssen has been granted a license agreement for the use of the EQ-5D-5L.

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

The WPAI©: GH will be administered at Randomization (Visit 2) and the Week 16 visit (Visit 8; and premature EDBT visit for participants who prematurely discontinue).

The WPAI©: GH [Section 14.9] is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to general health [Reilly 1993]. It has a recall period of 1 week.

Each individual participant will enter their scores on an electronic device. Written permission is neither required nor provided to researchers using the WPAI©: GH.

The WPAI©: GH will not be administered to illiterate participants, defined as participants who were unable to sign the ICF for themselves. It will also not be administered if the questionnaire is not available in a language that can be easily understood and read by the participant.

7.2.2.10 Patient Global Assessment of Disease Severity (PGA-S)

The PGA-S is a single item that asks participants to describe the severity of their PAH over the same 7 days as the PAH-SYMPACT™ was administered, with responses of “none,” “mild,” “moderate,” “severe,” and “very severe” [see Section 14.7].

The PGA-S is administered at Day 1/Visit 2 and Week 16 / EDBT (Visit 8) [or premature EDBT]. It is administered on an electronic device.

PGA-S will be administered to all participants screened after the implementation of PGA-S scale on the electronic device

7.2.2.11 Patient Global Impression of Change (PGI-C)

The PGI-C is a single item that asks the participant to rate the change of the patient's PAH since beginning of study treatment administration (Visit 2). The response options are "much better," "a little better," "no change," "a little worse," and "much worse" [see Section 14.7].

PGI-C will be administered to all participants with Week 16 visit occurring after implementation of PGI-C scale on the electronic device.

7.2.2.12 Semi-structured Qualitative Interview

An optional substudy with a semi-structured qualitative interview will be conducted in selected countries among participants that have reached the open-label treatment period of the study and provided specific consent to participate in this substudy. The objectives of this semi-structured qualitative interview substudy are to assess the participant's experience with M/T FDC treatment with regard to satisfaction with treatment, adherence to treatment, and convenience of treatment.

Interviews will be scheduled and conducted by an external vendor, who will ask clinical sites to share an enrollment log via a secure online file sharing platform which will include the names and contact information of the participants who have provided consent to participate in the qualitative interview. All interviews will be conducted in the participants' preferred language and last approximately 45 minutes.

An optional semi-structured qualitative interview will also be conducted with a subset of site Investigators to assess their experience of treating participants with M/T FDC . All interviews will be conducted in PI's preferred language and last approximately 20 minutes.

In the event that a participant reports possible adverse events during the qualitative interview, the trained interviewer, will report any potential AE as per Janssen's pharmaco-vigilance process and report them to the site/study physician within one business day of completing the interview. Sites will then evaluate the reported event(s) for AEs/SAEs based on procedures described in protocol Section 9.1and 9.2. The interviewer will also instruct the participant to contact their study physician (ie, Investigator) to report their concerns.

These interviews are semi-structured and designed to allow participants to provide their own impressions of the M/T FDC, thus the data will not be used within the study CSR. The content analysis will present qualitative themes that emerge from the narrative data. Data will be shared via secure file transfer protocols, or Health Insurance Portability and Accountability Act (HIPAA)/General Data Protection Regulation (GDPR) compliant platforms. Details of participant and Investigator semi-qualitative interview, including study design, interview guides, qualitative analysis plan, data retention and protection are provided in a separate standalone substudy manual.

7.2.2.13 Survival Follow-up

For all participants including those who prematurely discontinue the study at any time, survival information will be collected starting at the time of double-blind database lock (announced) and thereafter approximately yearly until death or study closure (ie, within 2 months prior to the last participants last visit [announced]) [Section 8.2]. The following information will be collected in the eCRF: vital status (including date and cause of death).

7.2.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs, and pregnancies are described in Section 9.

Note: All safety and tolerability assessments detailed below are to be performed up to 30 days after last intake of study treatment. For participants who enter a continued access program all safety and tolerability assessments are to be performed up to their EOS (see Section 3.1.1).

7.2.3.1 Concomitant Medications

Concomitant medications for a participant will be assessed at every visit. Changes in therapy or dose will be recorded in the eCRF.

7.2.3.2 Physical examination

See Table 4 and Table 5 for time points of assessment.

Physical examination (ie, inspection, percussion, palpation, and auscultation) includes the examination of general appearance (heart, lungs, abdomen, skin, extremities, eyes, ears, nose, throat, lymph nodes, nervous system, etc.).

Other exams will be performed if indicated, based on medical history and/or symptoms, as deemed necessary / indicated by the PI. Information for all physical examinations will be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing of informed consent must be recorded on the Medical History eCRF page. Physical examination findings made after signing of informed consent, which meet the definition of an AE [Section 9.1.1], must be recorded on the AE page of the eCRF.

7.2.3.3 Vital signs, weight, and height

See Table 4 and Table 5 for time points of assessment.

Non-invasive SBP and DBP and pulse measurements will be measured in a supine or sitting position. It is recommended to allow the participant to rest for at least 5 minutes, to perform the measurements, and to use the same device, same position (supine or sitting), same arm, same operator, and appropriate cuff size throughout the study for an individual participant.

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

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

If the results from the central laboratory are not available in time for randomization of the participant, an additional blood sample may be drawn to verify eligibility (eg, hemoglobin, kidney function, and LFTs) based on a local laboratory test. The local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF.

Other exceptional circumstances that will require recording of local laboratory results of the variables described in Section 7.2.4.2 (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 a central laboratory sample(s) is lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample(s) as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time window and these test results are available.

Central laboratory reports will be sent to the investigator. In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert sponsor personnel and the relevant site personnel. Alert flags that will trigger such notifications can be found in the laboratory manual.

All laboratory reports must be reviewed, signed, and dated by the investigator or delegate within 10 working days of receipt and filed as source documents. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of the ICF must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities detected after the signing of the ICF must be reported as an AE or SAE as appropriate [see Section 9], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.2.4.2 Laboratory tests

See Table 4 and Table 5 for time points of assessment.

During the double-blind treatment period, LFTs levels are monitored monthly. During the open-label treatment period, LFTs level monitoring is required monthly up to Visit 11 and every 3 months thereafter until EOLT. It is at the investigator's discretion to decide (taking into account the participant's medical history and AEs) if monthly tests after Visit 11 during the open-label treatment period are required/justified. Local laboratories may be used.

When LFT monitoring is performed between visits, a visiting nurse service may be used, if possible, to collect laboratory samples from the participant at home if available and allowed by local regulations. The visiting nurse service is to be provided by the sponsor and any laboratory samples collected in this fashion will be analyzed by the central laboratory. In exceptional circumstances a local laboratory affiliated with the site may be used and data recorded in the eCRF. If the local laboratory results show an increase in AST/ALT $\geq 3 \times$ ULN, the results must be reported in the eCRF, the participant must return to the site, and the AST/ALT re-test must be performed centrally.

Hematology

Rules for additional investigations and study treatment interruptions in case of hemoglobin abnormalities are provided in Section 5.1.11.

- Hemoglobin (SI Unit: g/L; conventional unit: g/dL).
- Hematocrit (SI Unit: L/L; conventional unit: %).
- Erythrocyte count (reticulocyte count) (SI Unit: 10^{12}/L; conventional unit: 10^{6}/μL).

- Leukocyte count with differential counts (SI Unit: 10^9/L; conventional unit: 10^3/μL).
- Platelet count (SI Unit: 10^9/L; conventional unit: 10^3/μL).

Clinical chemistry

Rules for additional investigations and study treatment interruptions in case of liver enzyme abnormalities or severe renal impairment are provided in Section 5.1.11.

- ALT (U/L).
- AST (U/L).
- Alkaline phosphatase (U/L).
- Total and direct bilirubin (SI unit: μmol/L; conventional unit: mg/dL).
- Creatinine (SI unit: μmol/L; conventional unit: mg/dL).
- Blood urea nitrogen (SI unit: mmol/L; conventional unit: mg/dL).
- Uric acid (SI unit: μmol/L; conventional unit: mg/dL).
- Glucose (SI unit: mmol/L; conventional unit: mg/dL).
- Sodium, potassium, chloride, calcium, magnesium (mmol/L).
- Total protein, albumin (SI unit: g/L; conventional unit: g/L).
- Albumin/globulin ratio.

The CKD-EPI 2009 equation [Levey 2009] is used for estimation of the creatinine clearance:

$$eGFR \quad 141 \times \min(S_{Cr}/K, 1)^{a} \times \max(S_{Cr}/K, 1)^{1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}.$$

Where:
eGFR (estimated glomerular filtration rate) mL/min/1.73m^2
S_{Cr} (standardized serum creatinine) mg/dL
K 0.7 (females) or 0.9 (males)
a 0.329 (females) or 0.411 (males)
min indicates the minimum of S_{Cr}/K or 1
max indicates the maximum of S_{Cr}/K or 1
age years

Coagulation tests

- Prothrombin time and/or International normalized ratio.
- Activated partial thromboplastin time.

Pregnancy test

A serum pregnancy test will be performed for women of childbearing potential at Screening and urine pregnancy tests will be performed monthly thereafter. The participants will be provided with validated urine pregnancy test kits by the site. The investigator/delegate will follow-up on the results of the urine pregnancy test with a 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 treatment should be discontinued until pregnancy is ruled out.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study Completion per Protocol

A participant who completes Week 16 of the double-blind treatment period, and the Safety Follow-up visit if he/she is not entering the open-label treatment period, is considered to have completed the study double-blind treatment period.

A participant who completes the full 120 weeks of the treatment and a Safety Follow-up visit is considered to have completed the study per protocol.

Study completion is reached once all participants have completed the EOS and is communicated to the sites via a study closure letter.

8.2 Premature Withdrawal From Study

Participants may voluntarily withdraw from the study without justification for any reason at any time. Participants are considered withdrawn if they state an intention to withdraw further participation in all components of the study (eg, withdrawal of consent), die, or are lost to follow-up. If a participant withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a participant from the study (without regard to the participant's consent) if, on balance, they believe that continued participation in the study would be contrary to the best interests of the participant. Withdrawal from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study.

Participants are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. The site must take preventive measures to avoid a participant being lost to follow-up (eg, document different ways of contact such as telephone number, home address, email address, person to be contacted in case the participant cannot be reached). If the participant cannot be reached, the site must make a reasonable effort to contact the participant, document all attempts, and enter the loss of follow-up information into the eCRF. The following methods must be used: at least 3 telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (eg, a visit by site personnel to the participant's home), respecting the participant's right to privacy. If the participant is still unreachable after all contact attempts listed above, they will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason (if known) for premature withdrawal from the study, along with who made the decision (participant, investigator, or sponsor personnel) must be recorded in the eCRF, if known.

If, for whatever reason (except death or loss-to-follow-up), a participant is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the participant, collect unused study treatment, and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the participants' medical records but will not be collected in the eCRF. The investigator must provide

follow-up medical care for all participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4. Survival status follow-up will be collected after the study discontinuation except for reason "withdrawal of consent" until death or study closure (Section 7.2.2.13).

8.3 Premature Termination or Suspension of the Study

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

If the study is prematurely suspended or terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with the sponsor must promptly inform all enrolled participants and ensure their appropriate treatment and follow-up, as described in Section 8.4. The sponsor may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participants' interests.

In addition, if the investigator suspends or terminates the participation of their site in the study without prior agreement from the sponsor, the investigator must promptly inform sponsor personnel and the IEC/IRB, and provide both with a detailed written explanation of the termination or suspension.

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

Any suspension or premature termination of the study must be discussed with the IDMC.

8.4 Medical Care of Subjects After Study Completion / Withdrawal From Study

After the participants' study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to the participants what treatment(s) / medical care is necessary and available according to local regulations.

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 insert M/T FDC becomes available during the study or program.

Participants who have completed the 24 months of the open-label period and are benefiting from the study intervention, as determined by their investigator, will be able to continue participation in the open-label period until alternative continued access is available in the patients country and as per local regulations via an open-label extension study or via post-study independent requests from their investigators if tadalafil 40 mg and macitentan 10 mg are not accessible for PAH in the patient's country.

Survival status follow-up will be collected after the study discontinuation until death or study closure (Section 7.2.2.13 and Section 8.2). Investigators may re-contact the participant to obtain

long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Section 12.3).

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse Events

9.1.1 Definition of adverse events

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

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from start of treatment until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the signing of informed consent form.
- Abnormal assessments, eg, change on physical examination, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, that was not present at study start, worsened during the course of the study, or led to dose reduction, interruption, or permanent discontinuation of study treatment.

Overdose of the study treatment and study treatment errors will be reported as an AE when associated with signs or symptoms.

9.1.2 Intensity of adverse events

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

As per Janssen SAE/AE reporting process, sites should record each AE separately if there is a change in intensity. Sites are to enter a stop date for the previous intensity and enter a new AE with start date to document when the change in intensity occurred. For AEs ongoing at the start of study treatment, if the intensity worsens after the start of study treatment, the change in intensity and the date on which it occurred must be reported in the eCRF.

The 3 categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

A mild, moderate, or severe AE may or may not be serious [see Section 9.3.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

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

9.1.3 Relationship to study treatment

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

9.1.4 Reporting of adverse events

All AEs with an onset date after the signing of the ICF and up to 30 days after study treatment discontinuation (up to EOS for participants who enter a continued access program on the same day as the EOS visit, see Section 3.1.1) must be recorded on specific AE pages of the eCRF.

9.1.5 Follow-up of adverse events and serious adverse events

AE/SAEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up information obtained after the participant's EOS visit will not be collected by the sponsor.

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

9.2 Serious Adverse Events

9.2.1 Definitions of serious adverse events

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

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

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for standard monitoring of a pre-existing disease or medical condition that did not worsen, eg, hospitalization for coronary angiography in a participant with stable angina pectoris.

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

9.2.2 Reporting of serious adverse events

All SAEs occurring after signature of the ICF up to 30 days after study treatment discontinuation (up to EOS for participants who enter a continued access program on the same day as the EOS visit see Section 3.1.1) must be reported on AE pages in the eCRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

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

9.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after study treatment discontinuation must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the participant's EOS visit / telephone call must be reported to the sponsor, but is not recorded in the eCRF.

9.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to the sponsor within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.2.5 Reporting procedures

All SAEs must be reported by the investigator to the sponsor within 24 hours of the investigator's first knowledge of the event.

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

The SAE forms must be sent to the sponsor (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment.

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

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The sponsor personnel may contact the investigator to obtain further information.

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

The expectedness of an adverse reaction is determined by the sponsor in the reference safety information (RSI) section provided in the IB. [Tadalafil SmPC] Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR and must be reported by the sponsor to concerned health authorities, IECs/IRBs, and investigators.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all 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.

9.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.3.1 Reporting of 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 SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention.

9.3.2 Follow-up of pregnancy

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

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the eCRF. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported on an SAE form as described in Section 9.2.5.

9.4 Product Quality Complaints

9.4.1 Definition

A 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.

9.4.2 Reporting 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.

9.5 Special Reporting Situations

Safety events of interest on the study treatment that require expedited reporting or safety evaluation include, but are not limited to:

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

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

9.6 Study Safety Monitoring

Study safety information (AEs, SAEs, laboratory values, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the sponsor Clinical Team (in charge of ensuring participants' safety as well as data quality). In addition, an IDMC monitors safety data [see Section 3.4]. The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (eg, medical imaging, local laboratory values) for the purpose of safety monitoring. Such additional anonymized data may be shared with external experts.

10 STATISTICAL METHODS

This study implements an adaptive group-sequential design with early futility and efficacy stopping rules and sample size re-estimation. It includes an IA (according to group-sequential design methodology) when approximately 100 participants have completed their EDBT assessment or have prematurely discontinued from the study.

If the study is not stopped early for futility or efficacy, a final analysis will be carried out when approximately 150 250 participants (based on conditional power considerations on PVR) have completed their EDBT assessment or prematurely discontinued from the study. The double-blind part of the study will then be reported. Study closure is defined as when the last participant performs their EOS visit. The double-blind and open-label parts will then be reported.

Conditional to positive outcome of the interim PVR results, all secondary endpoints will be formally evaluated according to the testing hierarchy. In case of negative outcome of the interim PVR results, secondary endpoints will only be evaluated at the final analysis according to the testing hierarchy.

A Statistical Analysis Plan (SAP) will be written and finalized before database cut-off and unblinding of the randomization codes by the IDMC for the IA. The SAP and IDMC charter will provide full details of the analyses, data displays, algorithms to be used for data derivations, and the IA decision-making process.

The SAP will include the definition of protocol deviations and the link between protocol deviations and the analysis sets. The protocol deviations will be identified by medically trained staff before study closure.

Individual participant listings will be provided for efficacy and safety endpoints, as well as for baseline and other participant characteristics. Each listing will be broken down by treatment group, stratum, site, participant number, and assessment date, where appropriate.

10.1 Analysis Sets

10.1.1 Screened Analysis Set

The Screened Analysis Set includes all participants who are screened and have a participant identification number.

10.1.2 All Randomized Analysis Set

The All Randomized Analysis Set includes all participants who were randomized in the study.

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who received at least one dose (for participants in FDC at least one dose of either macitentan or tadalafil) of study treatment.

Participants are evaluated according to the study treatment they have been assigned to, which may be different from the study treatment they have received.

10.1.4 Safety Set

The Safety Set (SS) includes all participants who received at least one dose of study treatment in the double-blind treatment period. Participants are evaluated according to the study treatment received. The treatment received will be different from the treatment assigned at randomization (randomized treatment) only in the case of a dispensing error that was sustained throughout the entire double-blind study period. Short-term dispensing errors will not qualify for a change from the randomized treatment group.

10.1.5 Open-label Set

The Open-label Set (OLS) includes all participants who receive at least one dose of open-label study treatment in the open-label period.

10.1.6 Combination Safety Set

The Combination Safety Set (CSS) includes all participants randomized to M/T FDC in the double-blind period and who received at least one dose of M/T FDC double-blind study treatment (ie, macitentan [10 mg] and tadalafil [20 mg or 40 mg]) and all participants who received at least one dose of M/T FDC study treatment (ie, macitentan [10 mg] and tadalafil [20 mg or 40 mg]) in the open-label period.

10.1.7 Long-term M/T FDC Set

The Long-term M/T FDC Set (LTFDCS) includes all participants randomized to M/T FDC in the double-blind study.

10.1.8 QoL analysis sets

The PAH-SYMPACT™ Symptoms Analysis Set includes all participants included in the FAS for whom at least one baseline value of symptoms domain is provided.

The PAH-SYMPACT™ Impacts Analysis Set includes all participants included in the FAS for whom at least one baseline value of impacts domain is provided.

The EQ-5D-5L Analysis Set includes all participants included in the FAS for whom at least one baseline value is provided.

The WPAI© Analysis set includes all participants included in the FAS for whom at least one baseline value is provided.

10.1.9 Usage of the analysis sets

The main analyses of the primary, secondary (except QoL variables), and other efficacy variables in the double-blind period will be performed on the FAS based on the treatment as randomized. The QoL variables will be analyzed based on PAH-SYMPACT™ Symptoms, PAH-SYMPACT™ Impacts, EQ-5D-5L, and WPAI© analysis sets, as applicable. The other efficacy variables that are assessed during the open-label period will be analyzed based on the OLS and LTFDCS.

The analyses of safety variables will be performed on the SS for the double-blind treatment period based on study treatment received as detailed in Section 10.1.4. The CSS will be used for the analyses of the safety variables in the entire study treatment period, including open-label treatment period.

Listings will be prepared on the FAS, unless otherwise specified. Participant disposition will be summarized for the randomized analysis set and the FAS.

10.2 Variables

10.2.1 Primary efficacy variable

The primary efficacy variable is the ratio of EDBT to baseline PVR and is assumed to follow a log-normal distribution. Consequently, the statistical analysis will be performed on the log of this ratio. The results will however be presented on the original scale (geometric means) after exponentiation of the means obtained on the log scale.

The PVR values (in dyn·sec·cm ^{5}) calculated by the sponsor [Section 14.1] will be used for the analysis.

If PVR value is missing at EDBT, it will be imputed according to the rules described in Section 10.3.2.4.

10.2.2 Secondary efficacy variables

10.2.2.1 6-minute walk distance

The variable for the analysis of the secondary endpoint, change from baseline to EDBT in exercise capacity, is the absolute change in 6MWD (m) from baseline to EDBT defined as:

- 6MWD (m) at EDBT 6MWD (m) at baseline

10.2.2.2 PAH-SYMPACT™ Symptom domains scores

The Symptoms part has 2 domains: Cardiopulmonary Symptoms Domain and Cardiovascular Symptoms Domain which contain 6 and 5 items, respectively.

Scores for the individual items and domains ranged from 0 4, with higher scores indicating greater symptom severity or worse impact. Mean weekly symptom item scores are calculated as an average of the daily item scores and a mean symptom domain score is then calculated as the average of the mean weekly scores for its included items.

Domain scores are set to missing if more than half of the respective item scores are missing. For more details on scoring algorithm including handling of missing item responses, see Section 14.5.

The main variables for the analysis of the secondary endpoint, change from baseline to EDBT in PAH-SYMPACT™ Symptoms domains scores, are the absolute changes from baseline to EDBT, defined as:

- Domain score at EDBT Domain score at baseline

10.2.2.3 WHO FC

Absence of worsening in WHO FC level at EDBT as compared to baseline is characterized based on the following dichotomous variable:

- Worsening: X 0 if (difference between EDBT and baseline in WHO FC) >0
- No worsening: X 1 if (difference between EDBT and baseline in WHO FC) ≤0

The secondary endpoint is the proportion of participants who remained stable or improved (no worsening) (X 1) between baseline and EDBT.

10.2.3 Other efficacy variables

See Section 6.1.3 for endpoint definitions. Additional details will be provided in the SAP.

10.2.4 Safety variables

The safety endpoints as defined in Section 6.2 will be presented according to the following 2 different treatment-emergent periods.

10.2.4.1 Double-blind treatment-emergent period

For the double-blind treatment period, treatment-emergent is defined from first intake of study treatment in double-blind period up to end of double-blind treatment + 30 days or start of open-label treatment, whichever occurs first.

10.2.4.2 Combination treatment-emergent period

The combination treatment-emergent period is defined from first intake of macitentan 10 mg and tadalafil (20 mg or 40 mg) in double-blind or open-label treatment period up to EOT (EDBT or EOLT) + 30 days. The baseline value for the combination treatment period is defined as the last valid assessment obtained prior to the first intake of macitentan and tadalafil (double-blind or open-label).

10.3 Description of Statistical Analyses

10.3.1 Overall testing strategy

The primary endpoint will be tested on the FAS using 2 analysis of covariance (ANCOVA) models separately comparing the combination group to each monotherapy. Only if both tests are statistically significant and M/T FDC is shown to be superior to both monotherapies will the study be declared to show conclusive evidence of efficacy.

Each null hypothesis will be tested (and family wise error rate preserved) during the IA using a Hwang, Shih and DeCani alpha spending function with gamma (γ) 2:

$$\alpha_1(t) \quad \alpha\ (1\text{-}\exp(\text{-}\gamma t))/(1\text{-}\exp(\text{-}\gamma)),$$

where t is the information fraction for a given pairwise comparison.

The alpha to be spent at the IA depends on the fraction of available information at the timing of the IA for each pairwise comparison, which depends on the recruitment process within each stratum. For each hypothesis, the information fraction is calculated individually based on the number of participants entering the test of the respective null hypothesis at the IA and on the number of participants originally planned for the final analysis. The earliest the IA can be performed when the global amendment 5 is approved in all countries. This is expected to occur when the information fraction (100/170) is 59% for each pairwise comparison. In this case, the alpha to be used will be 0.018 for both pairwise comparisons.

If the study is not terminated early, the inverse normal combination method will be utilized to combine first- and second-stage p-values for the control of the type-1 error rate [Lehmacher 1999]. The guideline for calculating the combination weights will be included in the IDMC charter (and SAP), and will be based on the available individual information fractions at the time of the IA. Combination weights will not be adjusted based on the IA decision. Median unbiased parameter estimates and repeated CIs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company).

Secondary efficacy endpoints will be analyzed at the $\alpha_1(t)$ level using a hierarchical testing procedure following the order of the endpoints as listed in Section 6.1.2.

Long-term efficacy data from the open-label phase will be analyzed descriptively.

10.3.2 Analysis of the primary efficacy variable

10.3.2.1 Estimand

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

A. Population: FAS (all randomized participants who received at least one dose (for participants in FDC at least one dose of either macitentan or tadalafil) of study treatment), as randomized.

B. Variable: Absolute change from baseline to EDBT visit of the log-transformed PVR values. The results will be presented on the original scale (geometric means) after exponentiation of the absolute mean changes obtained on the log scale.

C. Intercurrent events (events that preclude observation of the variable or affect its interpretation):

- Death occurring prior to the EDBT visit,
- Prohibited PAH-specific medication [see Section 5.2.4] received for any reason prior to EDBT visit,
- Study treatment discontinuation/interruption for more than 2 days immediately prior to the EDBT visit,
- Study treatment(s) dose adjustments at any time prior to the EDBT visit.

D. Population-level summary: Ratios of the geometric means between the M/T FDC group and each monotherapy group (macitentan 10 mg and tadalafil 40 mg) separately.

This estimand targets the effect of treatment initiation on the variable measurement prior to the occurrence of death or introduction of prohibited PAH-specific medication and follows a “while

on treatment" strategy. For purposes of the primary endpoint, on-treatment is defined as up to 2 days after last double-blind treatment intake.

Intercurrent events will be handled as follows:

- "Death occurring prior to the EDBT visit" will be addressed by imputing the EDBT PVR value using the rules defined in Section 10.3.2.4.
- "Prohibited PAH-specific medication received for any reason prior to EDBT visit" will be addressed by disregarding the PVR assessments obtained at the EDBT visit and imputing them with the rules defined in Section 10.3.2.4.
- "Study treatment discontinuation/interruption for more than 2 days immediately prior to the EDBT visit" will be addressed by disregarding the PVR assessments obtained more than 2 days after study treatment discontinuation and imputing them with the rules defined in Section 10.3.2.4.
- "Study treatment(s) dose adjustments at any time prior to the EDBT visit" will not lead to exclusion of on-treatment PVR assessments obtained at EDBT, and those values, if available, will be used in the primary analysis, otherwise they will be imputed with the rules defined in Section 10.3.2.4.

10.3.2.2 Hypotheses and statistical model

GM_{FDC} denotes the geometric mean of the ratios of EDBT to baseline PVR values for participants randomized to the M/T FDC group.

$GM_{macitentan\ 10\ mg}$ denotes the geometric mean of the ratios of EDBT to baseline PVR values for participants randomized to the macitentan 10 mg group.

$GM_{tadalafil\ 40\ mg}$ denotes the geometric mean of the ratios of EDBT to baseline PVR values for participants randomized to the tadalafil 40 mg group.

The global null hypothesis (H_O) is the union of 2 null hypotheses:

H_O: $H_{O1} \cup H_{O2}$,

where:

H_{O1} is "$GM_{FDC} / GM_{macitentan\ 10\ mg}$ 1" in the combined treatment-naïve and prior-ERA stratum,

H_{O2} is "$GM_{FDC} / GM_{tadalafil\ 40\ mg}$ 1" in the combined treatment-naïve and prior-PDE-5i stratum.

The global alternative hypothesis (H_1) is the intersection of 2 alternative hypotheses:

H_1: $H_{11} \cap H_{12}$,

Where:

H_{11} is "$GM_{FDC} / GM_{macitentan\ 10\ mg} \neq 1$" in the combined treatment-naïve and prior-ERA stratum,

H_{12} is "$GM_{FDC} / GM_{tadalafil\ 40\ mg} \neq 1$" in the combined treatment-naïve and prior-PDE-5i stratum.

Additional details about the strata are given in Section 10.5.

10.3.2.3 Treatment groups

For the comparison between M/T FDC and macitentan 10 mg, only participants randomized to M/T FDC or macitentan 10 mg in the treatment-naïve or prior-ERA strata will be included.

For the comparison between M/T FDC and tadalafil 40 mg, only participants randomized to M/T FDC or tadalafil 40 mg in the treatment-naïve or prior-PDE-5i strata will be included.

Data collected on participants who did not tolerate up-titration to tadalafil 40 mg and remained on tadalafil 20 mg or tadalafil 20 mg + macitentan 10 mg as separate tablets will be kept in the statistical analysis under the tadalafil 40 mg and M/T FDC arms respectively.

10.3.2.4 Handling of missing data

By design, only one post-baseline PVR measurement must be taken at the time of the scheduled EDBT visit. In some instances, the EDBT assessment may be missing with no other post-baseline assessment available.

If PVR cannot be calculated due to missing PAWP, the following conventions will be applied for the calculation at a visit at which both mPAP and CO are assessed and not missing:

1. If PAWP is missing, LVeDP will be used.
2. If PAWP and LVEDP are missing at post-baseline, the available baseline PAWP (or LVeDP) for the participant is used as a substitute for the missing post-baseline PAWP.

In the case of a missing PVR assessment at EDBT, the following missing data imputation rules will be used:

- If the participant dies prior to Week 16, the highest observed individual ratio of the last on-treatment PVR to the baseline PVR in the FAS, amongst all participants in the same stratum

is imputed, (or a value of 1 [ie, no change from baseline] is imputed if this worst observed value is an improvement [ie, decrease] from baseline).

- If the participant has a disease progression/worsening as confirmed by the CEC, the 75th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all participants in the same stratum will be used to impute the on-treatment PVR value.
- If the participant does not die and does not experience a disease progression/worsening as confirmed by the CEC, the 50th percentile of the ratio of the last on-treatment PVR to the baseline PVR from all participants in the same stratum and treatment group will be used to impute the on-treatment PVR value.

10.3.2.5 Main analysis

The null hypotheses will be tested by means of 2 ANCOVA models on the $\log_e$-transformed ratios of EDBT to baseline PVR values. Model covariates will include randomized treatment, the $\log_e$-transformed baseline PVR value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i). The resulting least squares (LS) means and 95% CLs obtained in each treatment group, and the LS-means differences (95% CLs) for M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg will be inversely transformed using the exponential function and multiplied by 100 to provide:

1. the adjusted geometric mean of the ratios of EDBT to baseline PVR values and corresponding 95% CLs, expressed in percent, in each treatment group, and
2. the adjusted geometric mean ratios (GMRs) and corresponding 95% CLs for M/T FDC vs macitentan 10 mg (GMR1) and for M/T FDC vs tadalafil 40 mg (GMR2).

The 2 p-values obtained from the tests of GMR1 and GMR2 (ie, the p-values for the LS-means differences) will be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg. The global null hypothesis will be rejected if both tests are significant at the appropriate alpha level according to the testing strategy detailed in Section 10.3.1. Median unbiased parameter estimates and repeated CLs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company).

10.3.2.6 Supportive/sensitivity analyses

i. Sensitivity analyses to assess the impact of missing values and their imputation

To assess the robustness of the model towards possible stratum or treatment-arm-related drop-out patterns, the following 3 sensitivity analyses for the primary endpoint will be conducted:

Sensitivity analysis 1: Repeat the primary imputation rule with the exceptions that the values to be imputed in case of death or disease progression have to be determined regardless of stratum instead of within the same stratum as defined for the primary analysis.

Sensitivity analysis 2: Use of multiple imputation where each missing value is replaced with a set of plausible values that represent the uncertainty about the right value to impute. Each one of the imputed data sets is analyzed using the same model as for the primary analysis and eventually aggregated using Rubin's rule [Rubin 1987].

Sensitivity analysis 3: A tipping-point analysis will be performed where missing data are replaced with a range of values to see how extreme the imputed value of the missing data must be for the results of the study to tip from significant to not significant.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

Sensitivity analysis 4: An observed case analysis applying the main ANCOVA model without any imputation [see Section 10.3.2.5].

ii. Sensitivity analyses for potential deviations from the normality assumptions

Sensitivity analysis 5: To address the impact of potential deviations from the assumption of normality of the residuals from the primary ANCOVA models, a rank-based linear model using Wilcoxon rank pseudo norm will be performed as follows:

- Missing EDBT values will be imputed as specified for the primary analysis in Section 10.3.2.4.
- A rank-based linear model will be performed on the primary variable (loge-transformed ratios of EDBT to baseline PVR values) using the Wilcoxon rank pseudo norm [Hettmansperger 2011] rather than the least squares pseudo norm. Model covariates will include randomized treatment, the loge-transformed baseline PVR value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i).

iii. Other sensitivity analyses

Sensitivity analysis 6: The primary endpoint analysis (ANCOVA) will be repeated without adjustment for the stratification factors.

iv. Other estimands

Five additional estimands will also be assessed:

- same as the primary estimand except that "prohibited PAH-specific medication received prior to EDBT visit" will not be considered as an intercurrent event and PVR assessments obtained after such an event will not be excluded from the analysis for that reason,
- same as the primary estimand except that on-treatment is defined as up to 7 days after last double-blind treatment intake instead of 2 days for the primary estimand,
- same as the primary estimand except that:
  - "prohibited PAH-specific medication received prior to EDBT visit" will not be considered as an intercurrent event and PVR assessments obtained after such an event will not be excluded from the analysis for that reason,
  - on-treatment is defined as up to 7 days after last double-blind treatment intake instead of 2 days for the primary estimand,
- same as the primary estimand except for the variable of interest which is the absolute change from baseline to EDBT in PVR instead of the ratio of EDBT to baseline PVR,
- same as the primary estimand except that in the population definition, participants are analyzed according to treatment received as opposed to treatment assigned.

10.3.3 Analysis of secondary efficacy variables

The primary estimands for each of the secondary endpoint variables defined in Section 10.2.2 follow the same approach as the primary endpoint estimand with the following exceptions:

- participants with missing baseline value are excluded,
- on-treatment is defined as up to 7 days after last double-blind treatment intake,
- assessments obtained in participants receiving prohibited PAH-specific medication for any reason prior to EDBT visit are *not* excluded from the analysis.

The rationale for handling intercurrent events differently for the secondary endpoint estimands compared to the primary endpoint is to minimize missing data. We allow a slightly wider window before exclusion of assessments as an immediate impact of prohibited PAH medication / study treatment discontinuation on the values being measured is not expected.

The primary endpoint estimand strategy will also be applied to the secondary endpoints as a sensitivity analysis.

10.3.3.1 Change from baseline to EDBT in 6MWD

The change from baseline to EDBT in 6MWD will be analyzed for each comparison of interest by means of an ANCOVA model and will include treatment group, baseline 6MWD value and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as covariates. The null hypothesis will be rejected upon achieving a statistically significant difference at a two-sided significance level of $\alpha_1(t)$ in favor of the FDC vs each monotherapy arm (macitentan 10 mg and tadalafil 40 mg). The 2 p-values obtained from each test (ie, the p-values for the LS-means differences) will be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg. The global null hypothesis will be rejected if both tests are significant at the appropriate alpha level according to the testing strategy. Median unbiased parameter estimates and repeated CLs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company). LS estimates for each treatment group and for the treatment effects (M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg) will be displayed with means, 95% CLs, and p-value.

The assumptions of the ANCOVA model (normality of the residuals and homogeneity of variance) will be investigated graphically (eg, Q-Q plot and residual plots). If there are major deviations from the assumptions, non-parametric tests will be conducted.

In the main analysis, if an EDBT assessment is missing for participants with a post-baseline 6MWD measurement obtained before EDBT, the (last) post-baseline 6MWD measurement will be carried forward unless this imputation would lead to an improvement, in which case a change of 0 m (no change) will be imputed. For participants without a post-baseline 6MWD measurement, a change of 0 m (no change) will be imputed. If the participant dies before Week 16, the lowest (worst deterioration) change from baseline recorded amongst all participants in the same treatment group will be imputed.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- An observed case analysis, applying the main ANCOVA without any imputation of missing EDBT assessments.
- An analysis applying the main ANCOVA without adjustment for the stratification factors.
- A mixed model repeated measure analysis of variance model performed on the FAS using the observed data up to EDBT, ie, at baseline, Week 8, and Week 16.

10.3.3.2 Change from baseline to EDBT in PAH-SYMPACT™ symptom domain scores

Change from baseline to EDBT in PAH-SYMPACT™ Symptom domain scores will be analyzed by means of ANCOVA, as described in Section 10.3.3.1.

In the main analysis, in case of a missing Symptom domain score at EDBT, the following missing data imputation rules will be used:

- If the participant dies prior to Week 16, the highest observed individual change of the last on-treatment Symptom domain score from the baseline score in the PAH-SYMPACT™ symptoms analysis set, amongst all participants in the same stratum is imputed, (or a value of 0 [ie, no change from baseline] is imputed if this worst observed value is an improvement [ie, decrease] from baseline).
- If the participant has a disease progression/worsening as confirmed by the CEC, the 75th percentile of the change of the last on-treatment Symptom domain score from the baseline score from all participants in the same stratum will be used to impute the on-treatment value.
- If the participant does not die and does not experience a disease progression/worsening as confirmed by the CEC, the 50th percentile of the change of the last on-treatment Symptom domain score from the baseline score from all participants in the same stratum and treatment group will be used to impute the on-treatment value.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the PAH-SYMPACT™ symptoms analysis set:

- Within the proposed imputation rules (see above), if the participant does not die and does not experience a disease progression/worsening, then multiple imputation method will be used to impute the missing scores. Each one of the imputed data sets will be analyzed using the same model as for the primary analysis and eventually aggregated using Rubin's rule [Rubin 1987].
- A tipping point analysis will be performed where missing data are replaced with a range of values to see how extreme the imputed value of the missing data must be for the results of the study to tip from significant to not significant.
- An observed case analysis, applying the main ANCOVA without any imputation of missing EDBT assessments.
- An analysis applying the main ANCOVA without adjustment for the stratification factors.
- An analysis applying the main ANCOVA and imputing the last observation carried forward (including the baseline score) in case of missing EDBT scores.

10.3.3.3 Proportion of subjects with no worsening in WHO FC between baseline and EDBT

The proportion of participants who improved or remained stable (absence of worsening) from baseline to EDBT in WHO FC (ie, a change ≤0) will be analyzed for each comparison of interest as a binary variable (no worsening vs worsening) by means of a logistic regression model. The model for the decrease from baseline to EDBT 'Yes/No' in WHO FC, representing a shift to a lower FC, will include treatment group, baseline WHO FC, and the stratification factor (treatment-naïve, prior-ERA, or prior-PDE-5i) as covariates. The null hypothesis will be rejected upon achieving a statistically significant difference at a two-sided significance level of $\alpha_1(t)$ in favor of the FDC vs each of monotherapy arm (macitentan 10 mg and tadalafil 40 mg). The 2 p-values obtained from each test (ie, the p-values for the LS-means differences) will be used to determine the superiority of M/T FDC vs macitentan 10 mg and tadalafil 40 mg. The global null hypothesis will be rejected if both tests are significant at the appropriate alpha level according to the testing strategy. Median unbiased parameter estimates and repeated CLs will be presented in the final analysis using ADDPLAN™ 6.1 (ADDPLAN, Inc., an Aptiv Solutions company). The adjusted odds ratio (OR) for the treatment effects (M/T FDC vs macitentan 10 mg and M/T FDC vs tadalafil 40 mg) will be displayed with 95% CLs and p-value. An OR above 1 can be interpreted as a larger improvement in WHO FC (or stable) occurring in the M/T FDC group compared to the reference group.

In the main analysis, if an EDBT assessment is missing, participants will be assumed to have worsened at EDBT.

To assess the impact of missing values and their imputation, the following sensitivity analyses will be run on the FAS:

- An observed case analysis without any imputation of missing EDBT assessments.
- In participants with a post-baseline WHO FC measurement obtained before Week 16, the post-baseline WHO FC measurement will be carried forward. This imputation will be performed unless the following occurs:
  - If a participant dies without a prior EDBT WHO FC assessment, then the EDBT WHO FC is imputed by class IV.

10.3.4 Sub-group analyses

In order to assess the consistency of the treatment effect across different participant subgroups, analyses will be performed on the primary endpoint and on the change from baseline to EDBT in 6MWD, PAH-SYMPACT™ symptom domains, and WHO FC, classifying participants according to relevant demographic characteristics.

The subgroups to be considered are:

- Geographical region (eg, US, Europe, Asia).
- Region (US, non-US).
- WHO FC (II vs III).

Analyses in subgroups on the FAS population are carried out the same way as on the entire population as described in Sections 10.3.2 and 10.3.3.1 for the primary endpoint and on the secondary endpoints, respectively. The treatment effects within subgroups will primarily be

displayed with their corresponding 95% CLs and presented in a forest plot. Treatment-by-subgroup interaction will be investigated by means of tests of heterogeneity.

In addition, the treatment effects of:

- M/T FDC vs each monotherapy arm will be assessed in the treatment-naïve stratum only;
- M/T FDC vs tadalafil 40 mg will be assessed in the prior-PDE-5i stratum only; and
- M/T FDC vs macitentan 10 mg will be assessed in the prior-ERA stratum only.

Further details will be provided in the SAP.

10.3.5 Analysis of the safety variable(s)

The safety analyses presented below will be performed using descriptive statistics on:

- The Safety Set for the double-blind treatment period. For these analyses, treatment-emergent period is defined in Section 10.2.4.1. Analyses will be presented by treatment groups as described in Section 10.3.2.3 and in addition for the pooled M/T FDC (ie, all participants treated with M/T FDC in the double-blind period across all 3 strata).
- The CSS for the combination treatment period. For these analyses, treatment-emergent period is defined in Section 10.2.4.2. Analyses will be presented by treatment received in the double-blind period:
  - Double-blind macitentan participants, ie, participants treated with macitentan monotherapy in the double-blind period.
  - Double-blind tadalafil participants, ie, participants treated with tadalafil monotherapy in the double-blind period.
  - Double-blind M/T FDC participants, ie, participants treated with combination of macitentan and tadalafil in the double-blind period.

Safety analyses may also be further presented by stratum (ie, treatment-naïve, prior-ERA, prior-PDE-5i).

All safety data will be listed, with flags for quantitative abnormalities. AEs in participants who were screened but not treated will be listed.

10.3.5.1 Adverse events

For the definition of AEs, see Section 9.1.1.

The number and percentage of participants experiencing treatment emergent AEs and SAEs at least once will be tabulated by:

- MedDRA SOC and individual preferred term within each SOC, in descending order of incidence.
- Frequency of participants with events coded with the same preferred term, in descending order of incidence.

Furthermore, treatment-emergent AEs, and SAEs will be tabulated as described above by intensity and relationship to study treatment.

The number and percentage of participants experiencing at least one treatment-emergent AE of special interest will be presented by descending Preferred Term frequency for each category of AE of special interest.

AEs leading to premature discontinuation of study treatment will be summarized as described above.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs and for AEs leading to premature discontinuation of study treatment.

10.3.5.2 Laboratory variables

For laboratory variables measured see Section 7.2.4.2.

Sponsor internal guidelines will be used for the definitions of marked abnormalities [Section 14.4]. All laboratory data will be transformed to standard units. All laboratory data transferred (provided by central or local laboratory) will be taken into account for identification of abnormalities regardless of whether they correspond to scheduled (per protocol) or unscheduled visits.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory variable providing their incidence and frequency.

10.3.5.3 Vital signs and body weight

Blood pressure (SBP and DBP), pulse rate, and body weight will be summarized at each study visit using the usual location and scale summary statistics for both absolute values and changes from baseline. Participants for whom no post-baseline value is available are excluded from the analysis of the changes from baseline.

10.4 Interim Analysis for Efficacy, Futility, and Adaptive Sample Size Re-estimation

One IA will be conducted when approximately 100 participants have completed their Week 16 assessment or have discontinued from the study prior to their Week 16 assessment. The IA will only include data from countries in which the global amendment 5 has been approved.

Differences in recruitment rates in each stratum will lead to different information fractions for the 2 pairwise comparisons at the time of the IA. The alpha spending for each pairwise comparison will hence not be the same. The recruitment rate in each stratum will be closely monitored in a blinded manner on an ongoing basis to appropriately quantify the actual IF for each comparison.

The IA will be conducted by the independent SSG on the primary endpoint to allow for early study termination due to overwhelming efficacy or futility, as well as for adaptive sample size re-estimation if the study is not terminated. The IDMC will review the interim results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC.

Hwang, Shih and DeCani alpha spending function with gamma (γ) 2 will be used to determine the required alpha levels for statistical testing which guarantee overall Type I error control in

presence of the multiplicity induced by the multiple looks at the primary endpoint. The calculations have been done in EAST 6.4 based on the formula:

$$\alpha_1(t) \quad \alpha\,(1\text{-}\exp(-\gamma t))/(1\text{-}\exp(-\gamma)),$$

where t is the information fraction for a given pairwise comparison.

Table 6 summarizes the alpha spent at the IA (with 100 participants) and final analysis for the scenario with recruitment rates proportional to the strata size and with 100 participants corresponding to 59% information fraction.

Table 6 Alpha spending in scenario with recruitment rates proportional to strata size

Look	Information fraction	Cumulative alpha spent	P-value
Interim analysis	59.0%	0.018	0.018
Final analysis	100%	0.05	0.042

If the study is not stopped for success, it may be stopped for futility (non-binding) if the conditional probability of reaching final study success is considered to be too low with the pre-planned sample size.

The sample size will be re-estimated at the IA based on unblinded effect estimates, following rules described in the IDMC charter. If the study is not terminated early for efficacy, the total size of the study shall not exceed N 250 participants and shall not be below N 150 participants, accounting for the overrun of participants recruited during the 16 weeks of follow-up.

The IDMC may recommend, based on the unblinded interim data, that the sponsor:

1. Stop the study for futility if the conditional success probability is <2.5% in either pairwise comparison, given the observed interim data.
2. Stop the study for efficacy if the interim test for PVR is positive for both pairwise comparisons at the two-sided $\alpha_1(t)$.
3. Continue the study with reassessed sample size, based on the conditional power, to a total between 150< N ≤250 participants.

Detailed guidelines for interim decision-making are further described in the IDMC charter. The boundaries to be used for the IA will depend on the actual information fraction and will be re-calculated by the independent SSG [Lehmacher 1999]. Any departure from the assumptions may lead to different stopping boundaries and decision-making rules.

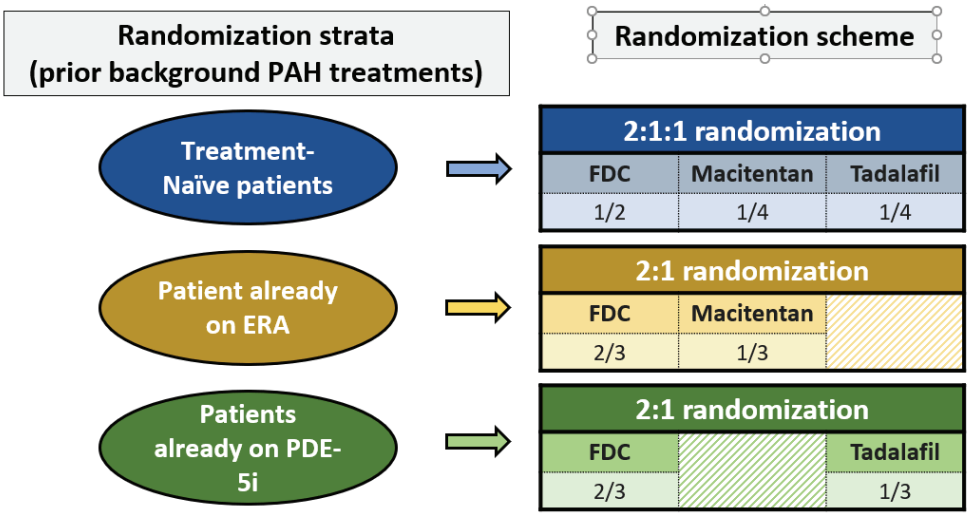
10.5 Sample Size

The sample size calculations presented in this section were carried out using East software version 6.4.

Randomization will be stratified by prior background PAH treatment at study entry (treatment-naïve, ERA, or PDE-5i). Treatment-naïve participants will be randomized 2:1:1 to M/T FDC,

macitentan, or tadalafil. ERA participants will be randomized 2:1 to M/T FDC or macitentan and PDE-5i participants will be randomized 2:1 to M/T FDC or tadalafil. Figure 3 shows the randomization scheme followed in this study.

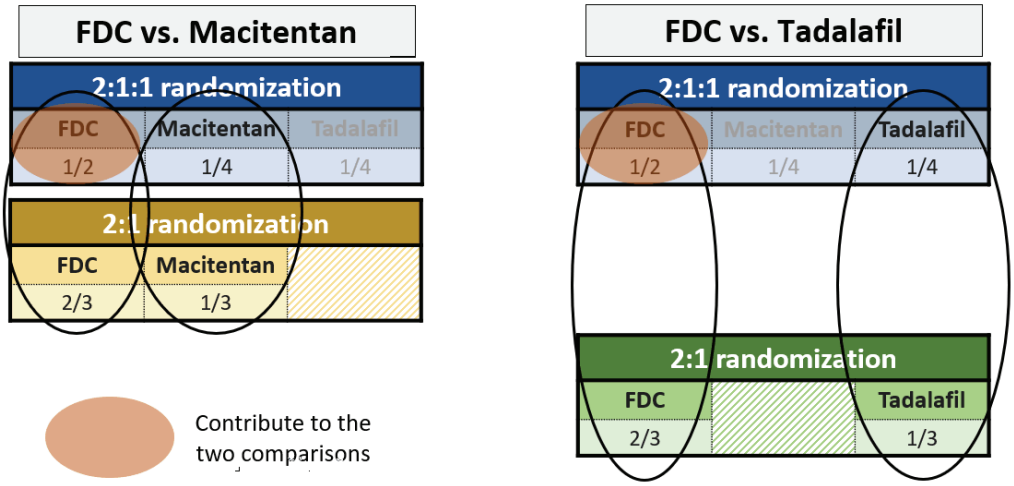
Figure 3 Randomization Scheme



ERA endothelin receptor antagonist; FDC fixed dose combination; PDE 5i phosphodiesterase type 5 inhibitor; Tx treatment.

The contribution of the randomization allocation of treatment to the strata to the 2 pairwise comparison of interest is illustrated in Figure 4.

Figure 4 Contribution of Randomization Treatment Allocation to the Comparison of Interest



According to the contribution of the randomization treatment allocation to the comparisons of interest and, as per current accrual projections (assuming 50 % naïve, 20% on ERA monotherapy and 30% on PDE5i therapy homogeneously over time) we expect approximately 98 participants to contribute to FDC vs. Macitentan 10 mg and approximately 115 participants for FDC vs. tadalafil 40 mg.

10.5.1 Sample size assumptions

Sample size is calculated based on the statistical requirements to detect a clinically relevant difference between the FDC group and both monotherapy groups using a 2:1 randomization ratio for each pairwise comparison. Each test comparing FDC to a monotherapy arm has a two-sided Type I error of 5% and a Type II error of 13% (87% power).

The following assumptions were made:

- the effect of FDC is assumed to be of similar extent vs each monotherapy and consistent across the treatment-naïve, prior-ERA, and prior-PDE-5i strata, ie, a ratio of geometric means of the EDBT / baseline PVR values equal to 0.75 for FDC vs the most efficient of the 2 monotherapies;
- a coefficient of variation of the ratio of 0.45;
- one IA is planned using an alpha spending function from the Hwang, Shih and DeCani class with gamma (γ) 2 [see Section 10.4]; and
- normal distribution for the $\log_e$-transformed ratio of EDBT to baseline PVR values.

If the 2 comparisons between the FDC and each monotherapy were completely statistically independent, the overall power of the test for the global null hypothesis would be 79.5%. It is, however, expected that those 2 tests are not independent and therefore that the overall power will be in excess of 79.5% up to a maximum of 86.8%.

These results are based on a difference in means test for independent samples with one interim analysis.

10.5.2 Sample size sensitivity

With a sample size of 98 for FDC vs macitentan 10 mg pairwise comparison (65 FDC vs 33 monotherapy), and sample size of 115 for FDC vs tadalafil 40 mg pairwise comparison (77 FDC vs 38 monotherapy), the power for showing superiority of FDC over macitentan 10 mg and of FDC over tadalafil 40 mg depends on the ratio of geometric means and the coefficient of variation of the percent of baseline PVR at EDBT. Table 7 displays power calculations for different assumptions for these 2 parameters and a two-sided α 0.05.

Table 7 Sample size sensitivity for the main analysis

Scenario	Ratio of GMs	CV	Power* FDC vs Maci	Power* FDC vs Tada	Overall power
Sensitivity 1	0.70	0.40	98.9%	99.6%	98.6% to 98.9%
Sensitivity 2	0.70	0.45	96.9%	98.5%	95.5% to 96.9%
Sensitivity 3	0.75	0.40	93.0%	96.1%	89.3% to 93.0%
Sample size assumptions	**0.75**	**0.45**	**86.8%**	**91.5%**	**79.5% to 86.8%**
Sensitivity 4	0.80	0.40	75.7%	82.1%	62.1% to 75.7%
Sensitivity 5	0.80	0.45	66.3%	73.3%	48.6% to 66.3%

* For each pairwise comparison between FDC and monotherapy, assuming that the monotherapies achieve the same therapeutic effect.
CV = coefficient of variation; FDC fixed dose combination; GM geometric mean.

11 DATA HANDLING

11.1 Data Collection

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture (using the RAVE system provided by Medidata Solutions Inc., a web-based tool). The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (ie, confirm the accuracy of the data recorded) using an electronic signature (refer to US 21 CFR Part 11).

Entries recorded by the participant in the patient-reported outcome questionnaires, either in written or electronic format, (PAH-SYMPACT™, EQ-5D-5L, WPAI©: GH, PGA-S, PGI-C) are considered source data.

Participant screening and enrollment data will be completed for all participants (ie, eligible and non-eligible) through the IRT system and the eCRF.

For each participant enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those participants who fail to complete the study. If a participant withdraws from the study, the reason must be noted on the eCRF.

11.2 Maintenance of Data Confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On CRFs or other documents (eg, documents attached to SAE forms / pregnancy forms) submitted to the sponsor and any CROs, participants must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other identifier. The investigator/delegate must keep a participant identification code list at the site, showing the screening/randomization number, the participant's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the participants (eg, signed ICFs) must not be sent to the sponsor, and must be kept in strict confidence by the investigator/delegate.

11.3 Database Management and Quality Control

eCRFs will be used for all participants. The investigators will have access to the site eCRF data until the database is closed. Thereafter, they will have read-only access for 6 months after database lock, after which data from the eCRF will be provided to the site using relevant storage media. The eCRF must be kept current to reflect participant status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by sponsor personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that participant confidentiality is protected.

This process will continue until database lock.

The central reading facility for RHC data will send results electronically to the study sponsor.

Laboratory samples will be processed through a central laboratory and the results will be electronically sent to the sponsor.

NT-proBNP samples will be processed through the central laboratory and the results will be sent electronically to the sponsor.

Testing of other biomarkers may happen after database lock and results will not be included in the clinical database.

AEs are coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA™) used by the sponsor.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate sponsor QS docs. After database lock, the investigator will receive the CRFs of the participants of his/her site (including all data changes made) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

Sponsor personnel and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the "Declaration of Helsinki", and with the laws and regulations of the country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the participant (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed Consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study and/or legally designated representative. The investigator/delegate must explain to participants that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific participant populations and of individual participants, as well as to the methods used to give the information. Finally, participants will be informed 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 re-contact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. Adequate time shall be given for the participant and/or legally designated representative to consider his or her decision to participate in the study and it shall be verified that the participant has understood the information (eg, by asking the participant to explain what is going to happen).

The ICF will be provided and administered in the respective country's local language(s).

Site personnel (according to local regulation) authorized to participate in the consent process and/or to obtain consent from the participant and/or legally designated representative will be listed on the Delegation of Authority form supplied by the sponsor. A study physician must always be involved in the consent process.

The participant and/or legally designated representative and authorized site personnel listed on the Delegation of Authority form supplied by the sponsor must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day as the informed consent is obtained) the ICF before any study-related procedures (ie, any procedures required by the protocol) begin.

A copy of the signed and dated ICF is given to the participant and/or legally designated representative; the original is filed in the site documentation. The informed consent process must be fully documented in the participant's medical records. This must include at a minimum the study reference, the participant number, the date and, if applicable, time when the participant was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the participant, and any additional person present during the consent process (eg, participant's family member[s]), and the information that a copy of the signed ICF was given to the participant/legally designated representative.

If the site intends to recruit participants who are considered as vulnerable (eg, participant cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure participant's rights are respected and the consent obtained is legally valid. The sponsor, the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to such recruitment. The consent process (eg, involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before participants are recruited.

12.4 Indemnification, Compensation and Refund of Expenses to Subjects and Investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The indemnification of the participant in the event of study-related injuries will comply with applicable regulations.

Study participants will be reimbursed for the study-related expenses (eg, travel costs, meals, hotel) to the extent permitted by applicable local regulations.

12.5 Protocol Adherence/Compliance

The investigator must conduct the study in compliance with the IEC/IRB and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the participant.

If a protocol deviation occurs, the investigator/delegate will inform the sponsor or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to the sponsor or (overruling) local requirements.

All major protocol deviations will be reported in the Clinical Study Report (CSR). IECs/IRBs will be provided with listings of protocol deviations per local requirements.

12.6 Protocol Amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

12.7 Essential Documents and Retention of Documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into 2 different categories of documents: ISF and participants' source documents.

These records must be kept by the investigator for as long as is necessary to comply with 'the sponsor's requirements (ie, as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

If the site is using an electronic/computerized system to store participant medical records, it can be used for the purpose of the clinical study if it is validated (per 21 CFR Part 11 or equivalent standard) and if the SM has been provided personal and restricted access to study participants only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store participant medical records but it could not be confirmed that the system is validated or if the SM could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by

the SM. The print-outs must be numbered, stapled together with a coversheet, signed, and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The print-outs will be considered as the official clinical study records and must be filed either with the participant's medical records or with the participant's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the SM must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The SM does not need to verify this process for all data of all participants but at least for some of them (eg, first participant; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some participants) per 'the sponsor's instructions. If it were not possible for the SM to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

12.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by the sponsor. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV.

The SIV must be completed before the site can start the screening of study participants. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the SM will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the CRFs and other protocol-related documents. Sponsor monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on participant recruitment rate and critical data collection times.

The PI must ensure that the eCRF is completed after a participant's visit (site visit or telephone call), and that all requested participant files (eg, ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the SM. The required site personnel must be available during monitoring visits and allow adequate time to meet with the SM to discuss study-related issues.

The investigator agrees to cooperate with the SM(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the participant is hospitalized or dies in a hospital other

than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active participants and all follow-up issues have been resolved. In case a site does not enroll any participants, the close-out visit may be performed prior to study database lock at the discretion of the sponsor.

12.9 Investigator Site File

Each site will be provided with an ISF prior to the SIV. It will contain all the essential documents that are required to be up-to-date and filed at site as per ICH-GCP Section 8.

The ISF will include a table of contents listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the SM regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from the sponsor. If the site needs to transfer the ISF to another location and/or if the site facility can no longer store the ISF, the PI must immediately inform the sponsor.

If the PI will change, or if the site will relocate, the SM must be notified as soon as possible.

12.10 Audit

The sponsor's representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to 'the sponsor's requirements (eg, standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (eg, participant records) and facilities.

12.11 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study (during the study or after its completion) at the site.

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform the sponsor (usually via the SM) that such a request has been made.

The investigator and site personnel must cooperate with the inspector(s) and allow access to all study documentation (eg, participant records) and study facilities.

12.12 Reporting of Study Results and Publication

The sponsor will post the key elements of this protocol and the summary of results on 'the sponsor's Clinical Trial Register and within the required timelines on publicly accessible databases (eg, clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by sponsor representatives and the Coordinating Investigator (or PI for single-center studies).

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

The Coordinating Investigator will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with sponsor personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement 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.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, the sponsor may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

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14 APPENDICES

14.1 Appendix 1 Sponsor Guidelines for the Right Heart Catheterization Procedure

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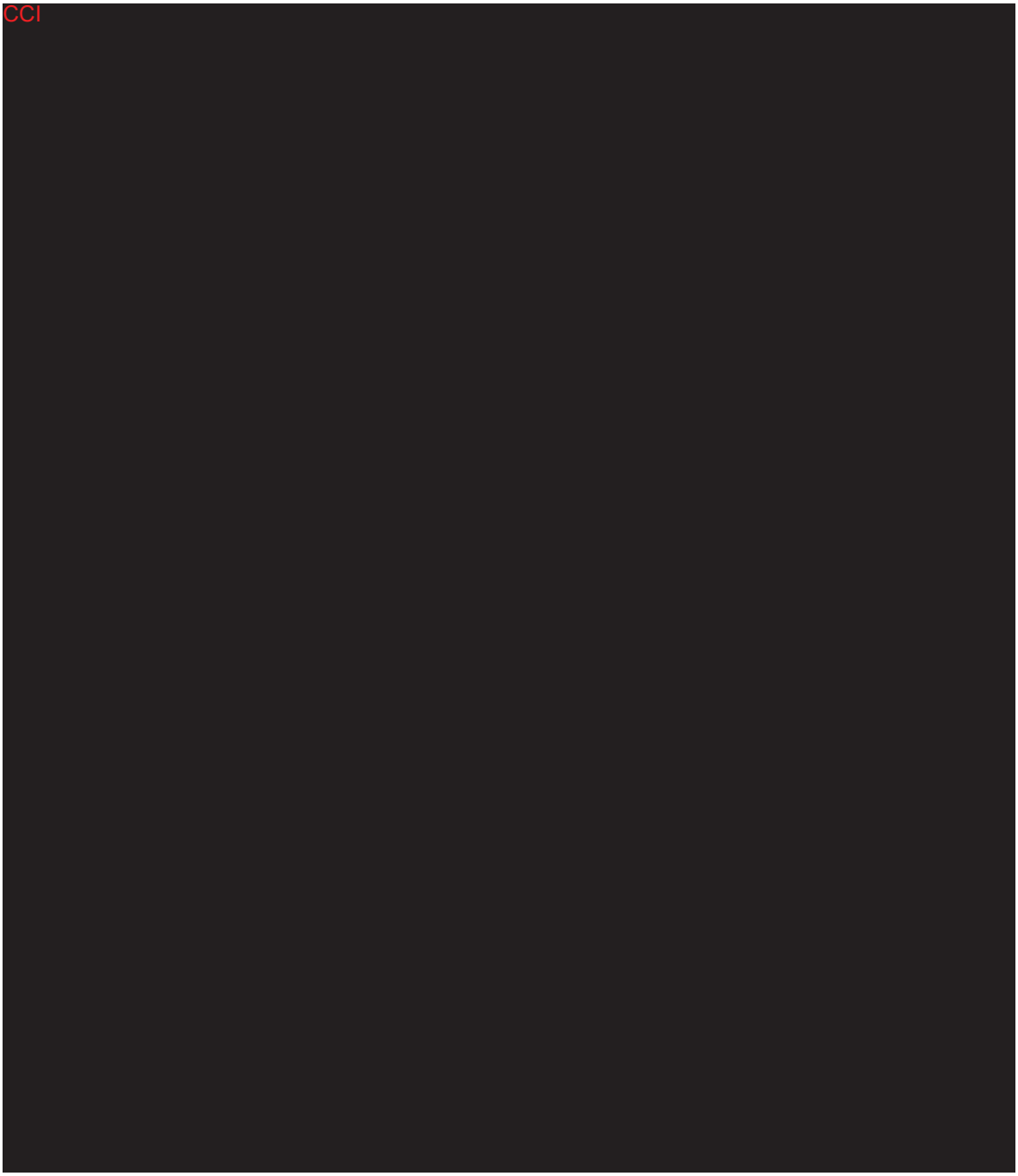

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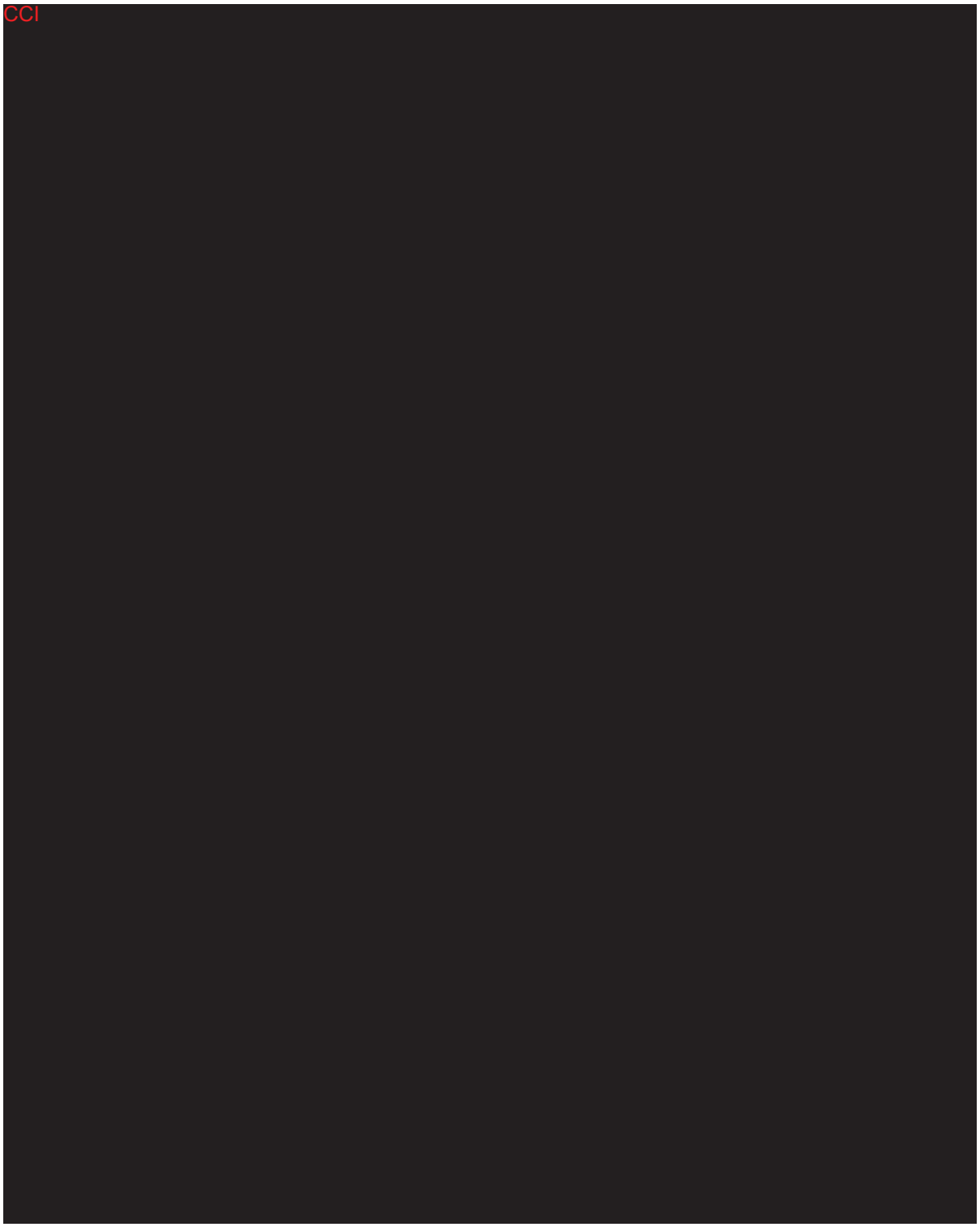

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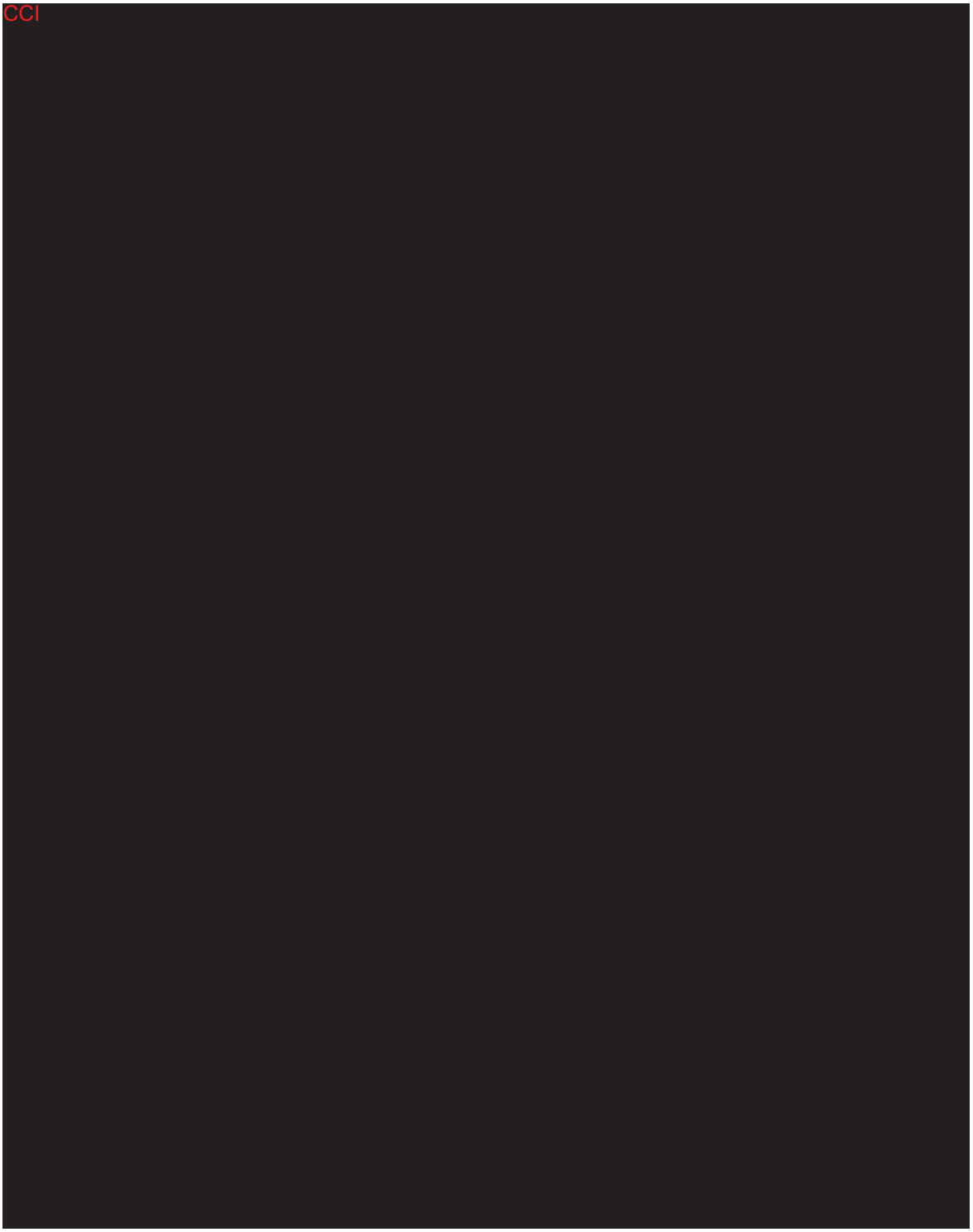

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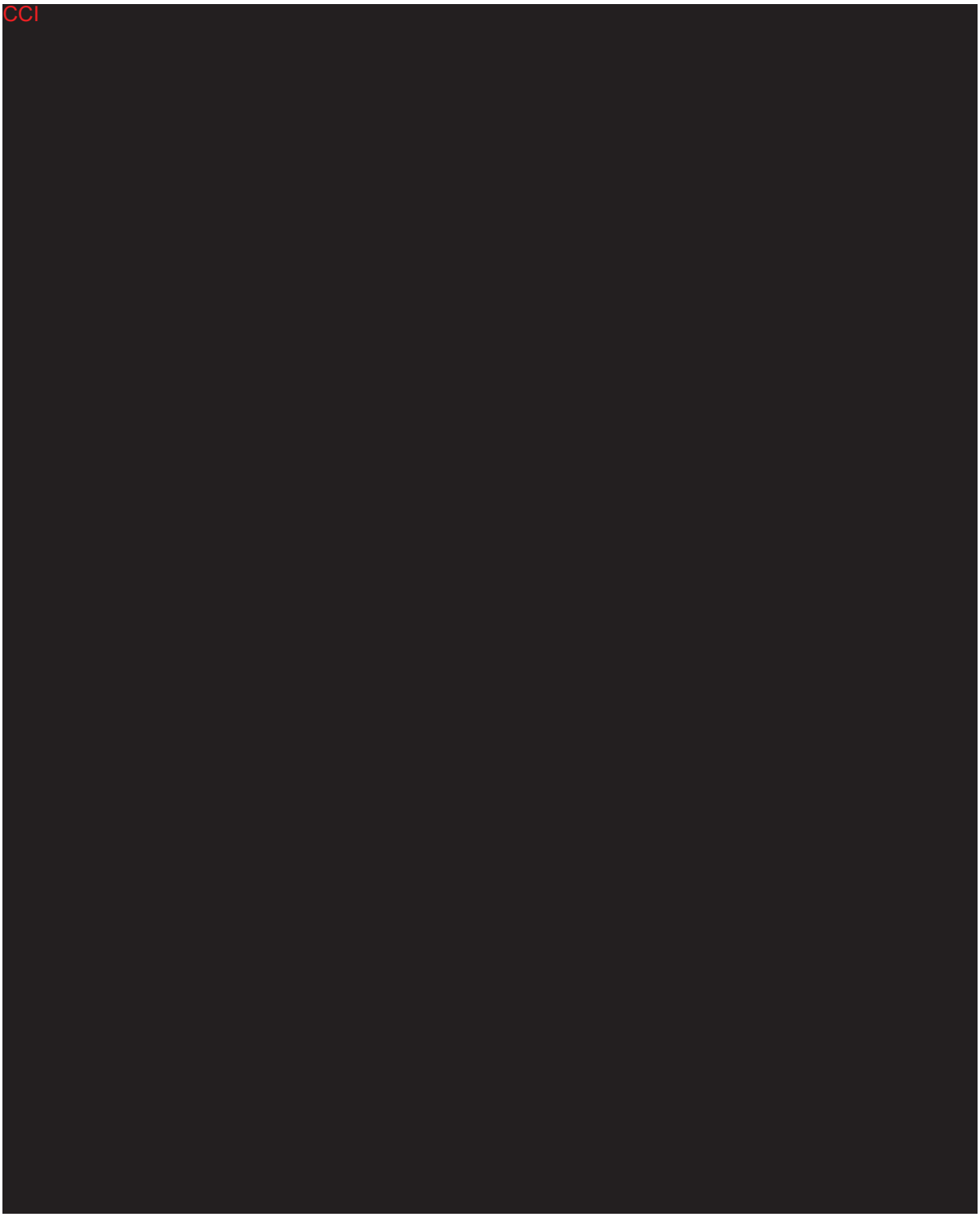

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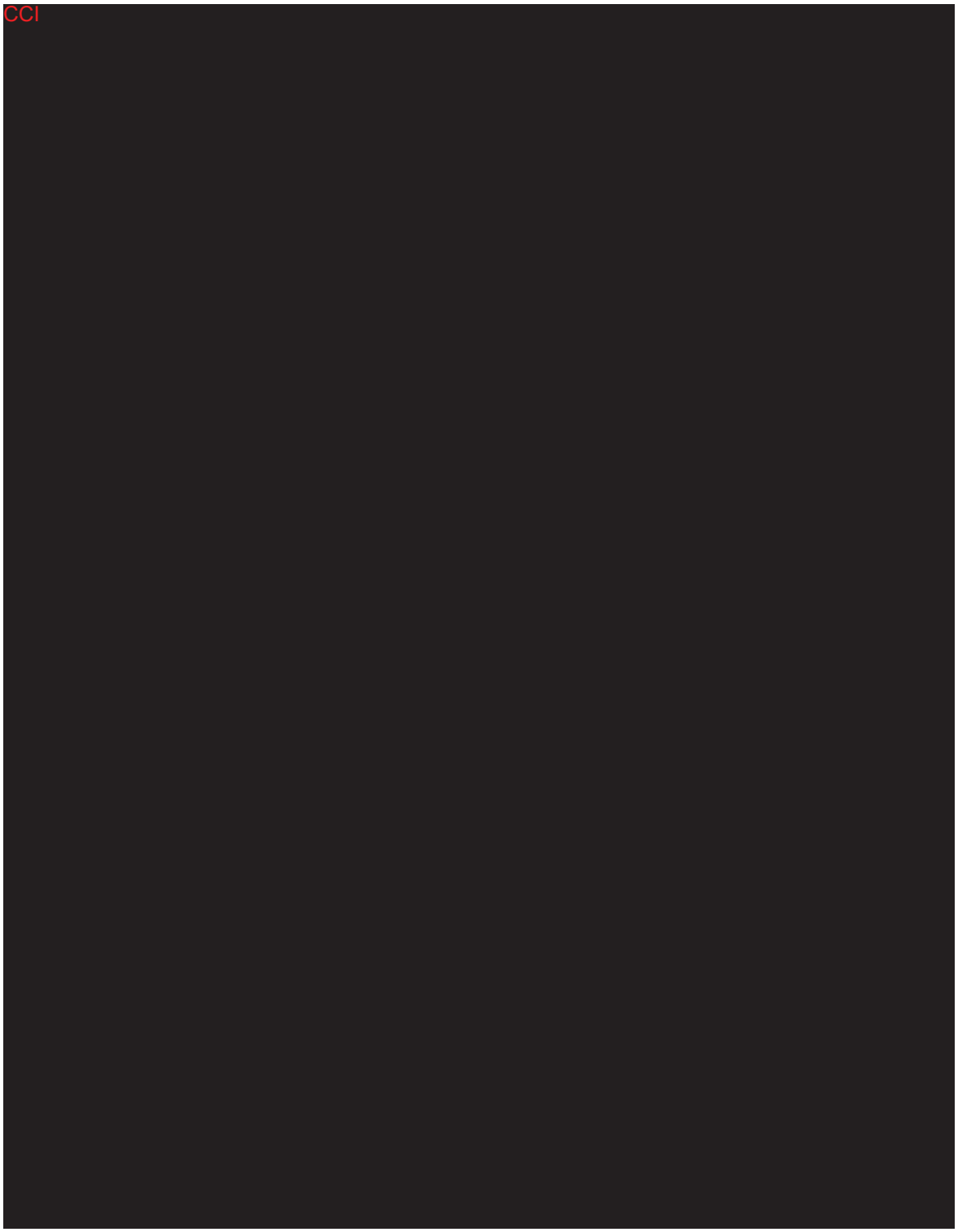

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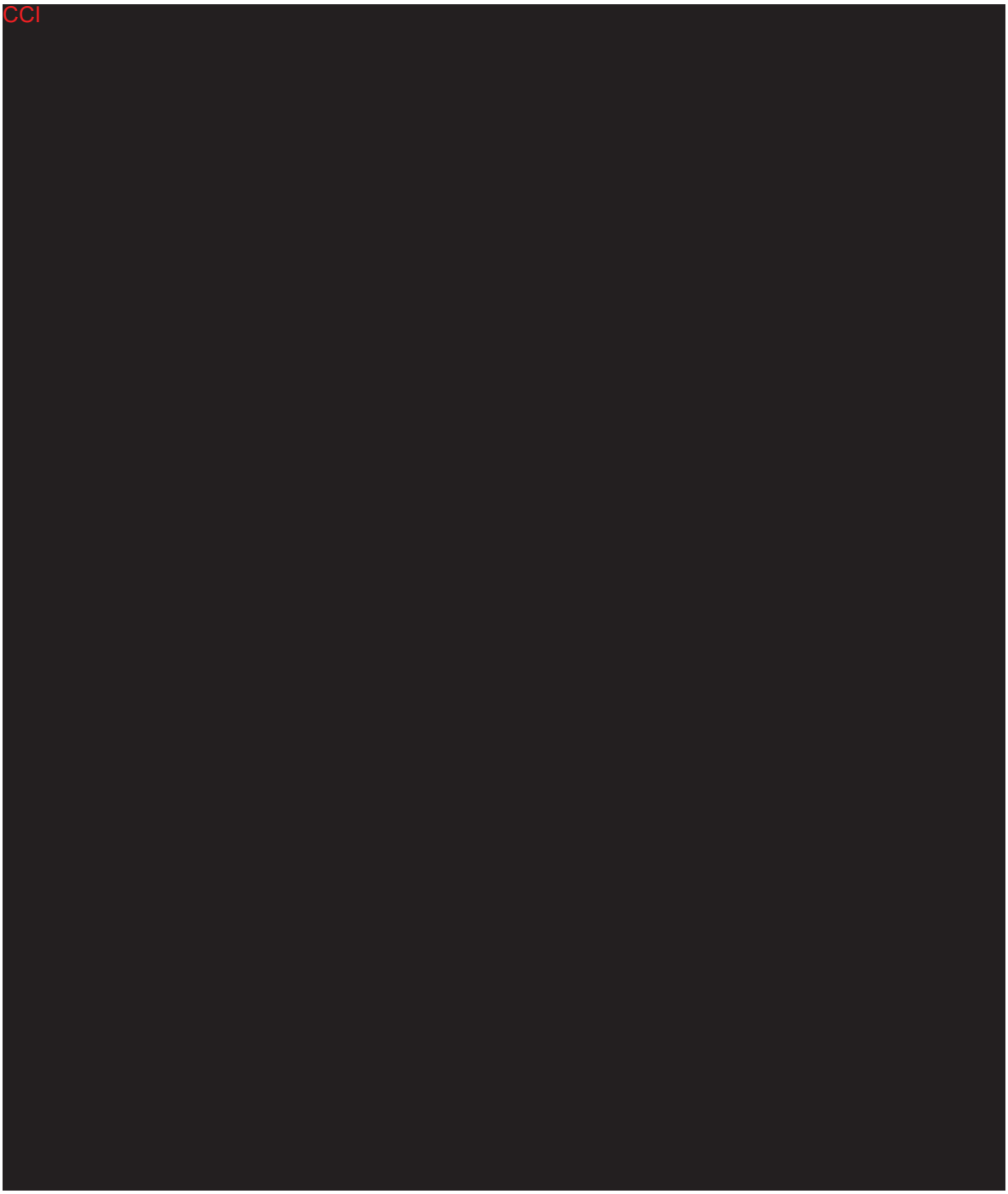


14.2 Appendix 2 Sponsor Guidelines for the 6MWT

14.2.1 INSTRUCTIONS

14.2.1.1 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 15 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. Ensure that the participant walks the same track on each 6MWT.

Local safety guidance 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 Section 14.2.3.1). 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 a 4-hour window of the baseline test) to minimize variability.

If a participant is oxygen dependent, the flow rate must remain constant from 1 hour 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.

14.2.1.2 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.

14.2.1.3 Timing

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

14.2.2 TEST REQUIREMENTS

14.2.2.1 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 10 minutes before the test starts.
- If the participant is used to take bronchodilators before a walk, he/she must take them 5 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.

14.2.2.2 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 CR10 Scale®

- Pulse oximeter

14.2.3 PERFORMING THE 6MWT

14.2.3.1 Instructions to the participant before the 6MWT

Before the 6MWT, the tester shows the Borg CR10 Scale®* to the participant and asks him/ her using the following dialogs:

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

If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and enter the values on the 6MWT worksheet.

* For consistency reasons, participants who were enrolled before the approval of Protocol AC-077A301 Amendment 2 Version 3 in their country must use the originally provided Borg Scale through the study and the tester uses the following dialogs:
"I would like to use the following scale to indicate the maximal shortness of breath you have now (indicate the Borg Scale).
Please grade your level of shortness of breath using this scale.
- *If there is no shortness of breath at all you would point to 0;*
- *if your shortness of breath is slight you would choose from 0.5 to 2;*
- *if your shortness of breath is moderate you would select 3;*
- *if the breathing is getting very difficult, you would choose 4 to 9, depending on just how hard or severe it is; 10 represents the most severe shortness of breath you have ever experienced in your life".*

14.2.3.2 Instructions to the participant during the 6MWT

The tester uses the following exact dialogue with the participant:

"The object 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. I will tell you when 2 minutes, 4 minutes have elapsed. Keep walking when I talk."

After these instructions are given to the participant, the tester then asks:

"Do you have any questions about the test?"

"Please explain what you are going to do."

"Are you ready?"

"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 tells the participant the time elapsed by saying:

"You have 4 minutes to go."

"You have 2 minutes 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 patient 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!"

14.2.3.3 Instructions to the participant 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.

The tester reminds the participant of their dyspnea that they chose before the 6MWT and asks them to rate his/her dyspnea using the Borg CR10 Scale®*. The tester uses the following dialogs:

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

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

* For consistency reasons, participants who were enrolled before the approval of Protocol AC-077A301 Amendment 2 Version 3 in their country must use the originally provided Borg Scale through the study and the tester uses the following dialogs:

"You have rated your shortness of breath as "xx" on this scale before the 6MWT. I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale).

Please grade your level of shortness of breath using this scale.

- *If there is no shortness of breath at all you would point to 0;*
- *if your shortness of breath is slight you would choose from 0.5 to 2;*
- *if your shortness of breath is moderate you would select 3;*
- *if the breathing is getting very difficult, you would choose 4 to 9, depending on just how hard or severe it is; 10 represents the most severe shortness of breath you have ever experienced in your life".*

If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and enter the values on the 6MWT worksheet.

14.2.4 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.

14.2.5 THE BORG SCALE [to be used for patients randomized under protocol versions 1 and 2]

Original Borg scale

For consistency reasons, participants who were enrolled before the approval of Protocol AC-077A301 Amendment 2 Version 3 in their country must use the originally provided Borg Scale through the study.

As soon as possible following the walk test, the participant is asked to rate his/her dyspnea using the Borg scale, tester will use the following dialog:

"You have rated your shortness of breath as "xx" on this scale before the 6MWT. I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg scale).

If there was no shortness of breath at all you would point to 0;

if the shortness of breath was not very great you would choose from 0.5 to 2;

if you were somewhat more short of breath you would select 3;

and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life."

0	NOTHING AT ALL
0.5	VERY, VERY SLIGHT (just noticeable)
1	VERY SLIGHT
2	SLIGHT (light)
3	MODERATE
4	SOMEWHAT SEVERE
5	SEVERE (heavy)
6	
7	VERY SEVERE
8	
9	
10	VERY, VERY SEVERE (maximal)

14.2.6 THE BORG CR10 SCALE® [to be used for patients randomized under protocol versions 3 and later]

The Borg CR10 Scale® must be printed on heavy paper (either DIN A4 or ANSI letter size and perhaps laminated) in 20 point type size.

The Borg CR 10 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 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?"

When rating dyspnea give a number that corresponds to how hard and strenuous you perceive your breathing to be[9]. 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.

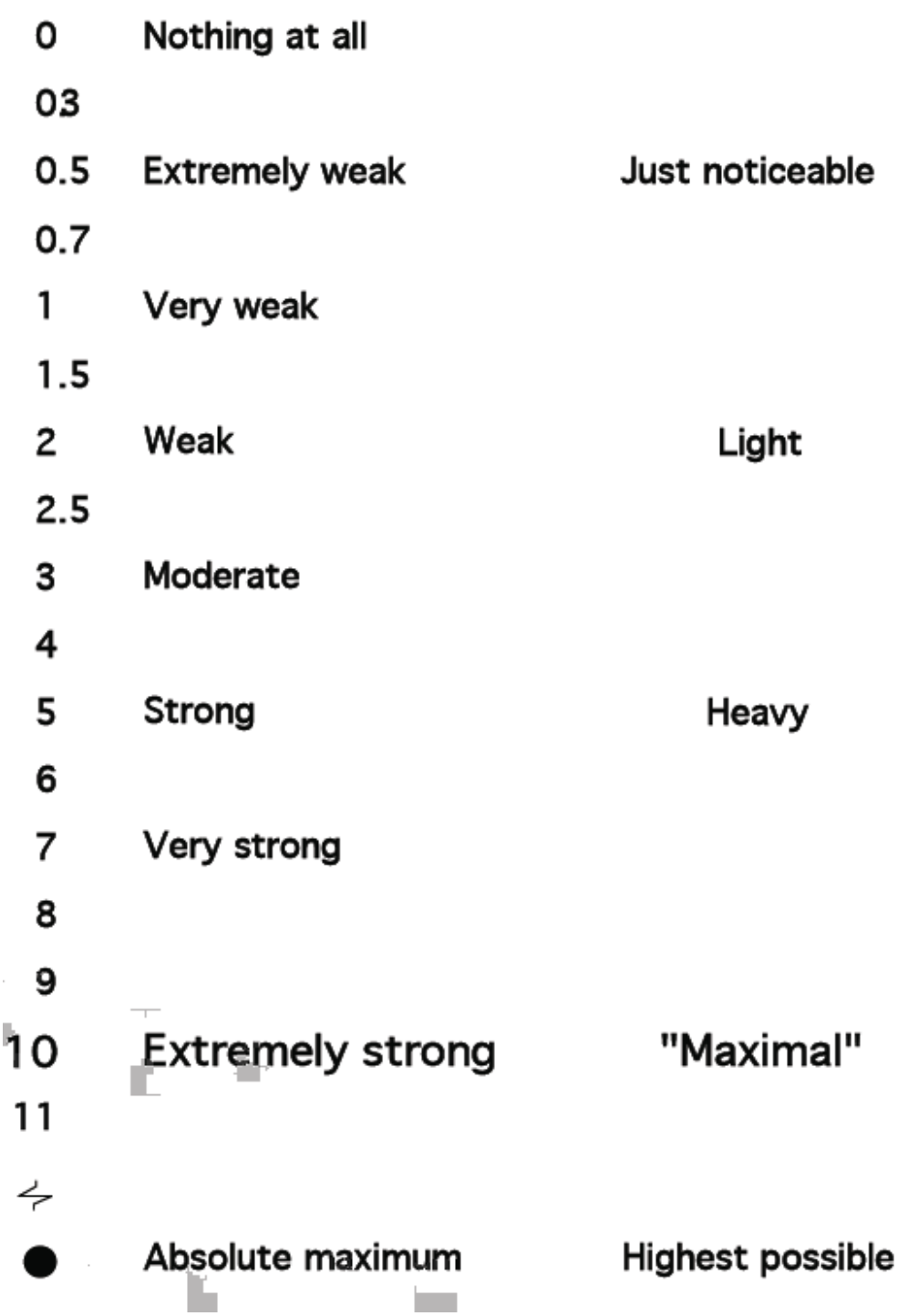
[9] The instructions for rating dyspnea have been customized by the Sponsor based on the instructions for rating exertion. These modifications have not been validated by Borg Perception AB.

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.


0
Nothing at all
03
0.5
Extremely weak
Just noticeable
0.7
1
Very weak
1.5
2
Weak
Light
2.5
3
Moderate
4
5
Strong
Heavy
6
7
Very strong
8
9
10
Extremely strong
"Maximal"
11
Absolute maximum
Highest possible

14.3 Appendix 3 WHO Functional 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.

14.4 Appendix 4 Marked Laboratory Abnormalities

Hematology (SI Units)

Laboratory test name (CDISC Synonym[s])	**LL**	**LLL**	**HH**	**HHH**
Hemoglobin	<100 g/L	<80 g/L	>20 g/L above baseline	>40 g/L above baseline
Hematocrit; EVF; PCV *(male)*	<0.32 L/L	<0.20 L/L	>0.60 L/L	>0.65 L/L
Hematocrit; EVF; PCV) *(female)*	<0.28 L/L	<0.20 L/L	>0.55 L/L	>0.65 L/L
Platelets *(assuming no platelet cluster)*	$<75\times10^9$/L	$<50\times10^9$/L	$>600\times10^9$/L	$>999\times10^9$/L
Leukocytes; white blood cells	$<3.0\times10^9$/L	$<2.0\times10^9$/L	$>20.0\times10^9$/L	$>100.0\times10^9$/L
Neutrophils (Abs)	$<1.5\times10^9$/L	$<1.0\times10^9$/L	NA	NA
Eosinophils (Abs)	NA	NA	$>5.0\times10^9$/L	NA
Lymphocytes (Abs)	$<0.8\times10^9$/L	$<0.5\times10^9$/L	$>4.0\times10^9$/L	$>20\times10^9$/L

EVF erythrocyte volume fraction; NA not applicable; PCV packed cell volume.

Blood chemistry (SI Units)

Laboratory test name (CDISC Synonym[s])	**LL**	**LLL**	**HH**	**HHH**
Alanine aminotransferase	NA	NA	>3 × ULN	>5 × ULN
Aspartate aminotransferase	NA	NA	>3 × ULN	>5 × ULN
Alkaline phosphatase	NA	NA	>2.5 × ULN	>5 × ULN
Bilirubin; Total bilirubin	NA	NA	>2 × ULN	>5 × ULN
Creatinine	NA	NA	>1.5 × ULN	>3 × ULN
Sodium	NA	<130 mmol/L	>150 mmol/L	>155 mmol/L
Potassium	<3.2 mmol/L	<3.0 mmol/L	>5.5 mmol/L	>6.0 mmol/L
Creatinine clearance	<60 ml/min	<30 ml/min	NA	NA

NA not applicable; ULN upper limit of normal.

14.5 Appendix 5 PAH-SYMPACT™ Questionnaire

14.5.1 Administration and Scoring

14.5.1.1 Administration

The PAH-SYMPACT™ is composed of 2 parts: the Symptoms part, which is administered daily for 7 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 2 domains plus one question about oxygen use. There is no total symptom score; the 2 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 7 consecutive days.

The Impact part contains 11 items across 2 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.

14.5.1.2 Scoring

Items have a five-point Likert response scale; responses are transcribed to numerical values [see Table 8 below] for further analyses.

Table 8 Symptoms (n 11)

Cardiopulmonary symptoms Domain	
1. How would you rate your shortness of breath?	No shortness of breath at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
2. How would you rate your fatigue?	No fatigue at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4

3. How would you rate your lack of energy?	No lack of energy at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
4. How would you rate the swelling in your ankles or legs?	No swelling in ankles or legs at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
5. How would you rate the swelling in your stomach area?	No swelling in stomach area at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
6. How would you rate your cough?	No cough at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
Cardiovascular Symptoms Domain	
7. How would you rate your heart palpitations (heart fluttering)?	No heart palpitations (heart fluttering) at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
8. How would you rate your rapid heartbeat?	No rapid heartbeat at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
9. How would you rate your chest pain?	No chest pain at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4

10. How would you rate your chest tightness?	No chest tightness at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4
11. How would you rate your lightheadedness?	No lightheadedness at all = 0 Mild = 1 Moderate = 2 Severe = 3 Very Severe = 4

Table 9 Impacts (n 11)

Physical Impacts Domain	
1. Were you able to walk slowly on a flat surface?	Yes, with no difficulty at all = 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4
2. Were you able to walk quickly on a flat surface?	Yes, with no difficulty at all= 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4
3. Were you able to walk uphill?	Yes, with no difficulty at all= 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4
4. Were you able to carry things, such as bags or baskets?	Yes, with no difficulty at all = 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4
5. Were you able to do light indoor household chores such as preparing food, cleaning surfaces, or tidying up?	Yes, with no difficulty at all = 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4
6. Were you able to wash or dress yourself?	Yes, with no difficulty at all = 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4

7. How much did you need help from others?	Not at all = 0 A little bit = 1 Some = 2 Quite a bit = 3 Very much = 4
Cognitive/Emotional Impacts Domain	
8. Were you able to think clearly?	Yes, with no difficulty at all = 0 Yes, with a little difficulty = 1 Yes, with some difficulty = 2 Yes, with much difficulty = 3 No, not able at all = 4
9. How sad did you feel?	Not at all = 0 A little bit = 1 Somewhat = 2 Very = 3 Extremely = 4
10. How worried did you feel?	Not at all = 0 A little bit = 1 Somewhat = 2 Very = 3 Extremely = 4
11. How frustrated did you feel?	Not at all = 0 A little bit = 1 Somewhat = 2 Very = 3 Extremely = 4

14.5.1.3 Symptoms

Individual mean weekly symptom item scores are determined across the days in a given week (ie, the mean score for symptom 1 is the sum of the 7 days divided by the number of days with non-missing data).

Each mean weekly symptom item score by definition has to range from 0 4.

No more than 3 missing days are allowed per week (can be consecutive or non-consecutive).

The mean individual weekly symptom item scores are aggregated by domain, with the sum then being divided by the number of symptom items in the respective domain.

This leads to the average weekly domain score ranging from 0 4 for each patient.

The group-level domain scores are calculated by summing the individual domain scores and taking the mean.

14.5.1.3.1 Missing data

If 2 adjacent responses (eg, mild and moderate) are both marked, the item score defaults to the worst (ie, moderate). Electronic versions of the questionnaire should be programmed so that only one response may be selected. Therefore, this should not occur unless the instrument is administered via paper-pencil.

If more than one response is selected and they are not adjacent, the item is missing. Electronic versions of the questionnaire should be programmed so that only one response may be selected. Therefore, this should not occur unless the instrument is administered via paper-pencil.

Domains with an even number of items can be scored as long as half of the items are completed; for domains with an odd number of items, half plus one item must be completed.

14.5.1.4 Impacts

Individual impact item scores are aggregated by domain, with the sum divided by the number of impact items in the respective domain.

The weekly domain score ranges from 0 4 for each patient.

The group-level domain scores are calculated by summing the individual domain scores for all of the patients and taking the mean.

14.5.1.4.1 Missing data

If 2 adjacent responses (eg, not at all and a little bit) are both marked, the item score defaults to the worst (ie, a little bit). Electronic versions of the questionnaire should be programmed so that only one response may be selected. Therefore, this should not occur unless the instrument is administered via paper-pencil.

If more than one response is selected and they are not adjacent, the item is missing. Electronic versions of the questionnaire should be programmed so that only one response may be selected. Therefore, this should not occur unless the instrument is administered via paper-pencil.

Domains with an even number of items can be scored as long as half of the items are completed; for domains with an odd number of items, half plus one item must be completed.

14.5.2 Sample Questionnaire

Pulmonary **A**rterial **H**ypertension-**Sym**ptoms and Im**pact (PAH-SYMPACT®)**
Questionnaire

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.

SYMPTOMS *(Day 1)*

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.**

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. Rate each symptom "at its worst".**

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

Continue onto the next page

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

INSTRUCTIONS *(Day 7)*

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

Continue onto the next page

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

Continue onto the next page

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 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

Continue onto the next page

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

14.6 Appendix 6 EQ-5D-5L

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐

SELF-CARE

I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

USUAL ACTIVITIES *(eg work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐

PAIN / DISCOMFORT

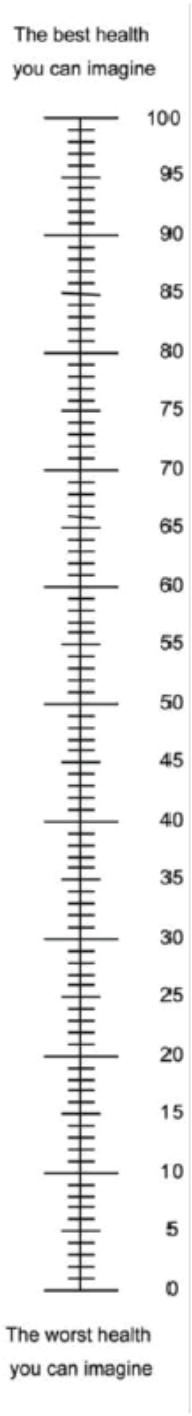
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

ANXIETY / DEPRESSION

I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



14.7 Appendix 7 PGA-S and PGI-C Scales

14.7.1 Patient Global Assessment of Disease Severity (PGA-S)

Please choose the response that best describes the severity of your PAH symptoms over the past 7 days. (Choose one response)

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

14.7.2 Patient Global Impression of Change (PGI-C)

Please choose the response below that best describes the overall change in your PAH symptoms since you started taking the study medication.
(Choose one response)

- ☐ Much Better
- ☐ A Little Better
- ☐ No Change
- ☐ A Little Worse
- ☐ Much Worse

14.8 Appendix 8 Model for End-stage Liver Disease (MELD) Score

MELD $3.78 \times \log_e$ serum bilirubin (mg/dL) +

$11.20 \times \log_e$ international normalized ratio +

$9.57 \times \log_e$ serum creatinine (mg/dL) +

6.43 (constant for liver disease etiology)

Notes:

If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0.

Any value less than 1 is given as a value of 1 (ie, if bilirubin is 0.8, a value of 1.0 is to be used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result).

14.9 Appendix 9 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI©: GH) V2.0

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 7 days**, not including today.

2. During the past 7 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 7 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 7 days, how many hours did you actually work?

_____HOURS (If "0", skip to question 6.)

5. During the past 7 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 7 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

14.10 Appendix 10 Study Conduct During a Natural Disaster

Information on managing the impact of the Coronavirus Disease 2019 (COVID-19) pandemic on the study is described in the COVID-19 Appendix (EDMS-RIM-264821, version 3.0).

14.11 Appendix 11 Protocol Amendment History

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

Amendment	Date	Main Reasons
1	12 Aug 2019	1. Eligibility criteria for hemodynamics will be confirmed by the central reading. 2. Change the objective of the evaluation of PAH symptoms and their impact on participant's life from secondary to "other" objective. 3. Update frequency of liver function test monitoring. 4. Update plan for follow-up of participants who prematurely discontinue study treatment.
2	28 Feb 2020	To implement updated guidelines for the right heart catheterization and 6MWT procedures in order to facilitate alignment in RHC and 6MWT procedures and data collection across all Actelion trials
3	17 July 2020	To update an exclusion criteria and concomitant therapy section pertaining to newly identified drug-drug interactions (DDI) between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 and CYP2C9) from a pre-clinical study on implications of role of CYP2C9 in the metabolism of macitentan.
4	20 October 2020	To move the cardiopulmonary and cardiovascular domain scores of the PAH-SYMPACT™ from exploratory endpoints to secondary endpoints following discussion with the Food and Drug Administration (FDA).
5	27 April 2021	To change the requirements on the minimum number of participants in each stratum (iea, treatment-naïve, prior-endothelin receptor antagonists [ERA]; prior-Phosphodiesterase type-5 inhibitor [PDE5i]) at the interim and final analyses.

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: (Please add the name here)

Name (typed or printed): PPD .

Institution: Janssen Research & Development

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

(Day Month Year)

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

Signature

User	Date	Reason
PPD	21-Nov-2022 12:42:28 (GMT)	Document Approval
PPD	21-Nov-2022 12:53:56 (GMT)	Document Approval
PPD	21-Nov-2022 14:07:01 (GMT)	Document Approval