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

Selexipag / ACT-293987

Chronic Thromboembolic Pulmonary Hypertension

Protocol AC-065B302

SELECT: SELExipag in inoperable or persistent/recurrent Chronic Thromboembolic pulmonary hypertension

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, group-sequential, adaptive, Phase 3 study with open-label extension period to assess the efficacy and safety of selexipag as an add-on to standard of care therapy in subjects with inoperable or persistent/recurrent after surgical and/or interventional treatment Chronic Thromboembolic Pulmonary Hypertension.

Study Phase:	3
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Actelion document number (Doc No.):	D-20.234

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SPONSOR CONTACT DETAILS

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Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
Medical Emergency Hotline Toll phone number: [number]	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File

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

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Doc No D-20.234

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called the sponsor

Treatment name / number

Selexipag / ACT-293987

Indication

Chronic Thromboembolic Pulmonary Hypertension

Protocol number, study acronym, study title

AC-065B302, SELECT: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, group-sequential, adaptive, Phase 3 study with open-label extension period to assess the efficacy and safety of selexipag as an add-on to standard of care therapy in subjects with inoperable or persistent/recurrent after surgical and/or interventional treatment Chronic Thromboembolic Pulmonary Hypertension.

I approve this protocol.

Title	Name	Date	Signature
PPD			

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INVESTIGATOR SIGNATURE PAGE

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

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

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Independent Ethics Committee or Institutional Review Board (IEC/IRB) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the subjects (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Site Manager(s) (SM[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all subjects or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk-benefit balance for an individual subject. I confirm

herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

	Country	Town	Date	Signature
Principal Investigator				

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3, Version 4	29-Sep-2020
Amendment 2, Version 3	16-Apr-2020
Amendment 1, Version 2	09-Jan-2019
Original Protocol, Version 1	30-Jul-2018

Amendment 3, Version 4 (29 September 2020)

Overall Rationale for the Amendment: The overall rationale for the amendment is to update the information regarding the resolutions made to biostatistical evaluation section in response to Food and Drug Administration (FDA) queries, to update safety reporting requirements to align with Janssen process as well as to make minor updates, corrections, and editorial document formatting revisions.

Section Number and Name	**Description of Change**	**Brief Rationale**
Synopsis; 3.1 Study design	The number of study sites was updated to 195 (earlier 175).	To update the number of study sites.
Synopsis; 3.1.2 Study duration; 3.2.2 Rationale for the duration of the study; 10.6.3 Time to clinical worsening (according to the CHMP definition)	The maximum duration for double blind (DB) phase is revised to **59** months from previous 52 months. The maximum duration of participation of a subject in the study is updated to approximately **74** months (earlier 67 months).	The required number of clinical worsening events is increased due to the smaller alpha level in the new testing strategy. To update duration of study participation.
Synopsis; 4.3 Inclusion criteria	It was clarified that subjects with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after balloon pulmonary angioplasty (BPA) are also to be deemed inoperable.	Reworded to avoid misunderstanding towards the following stratification group: "inoperable [with or without BPA]".
5.1.6 Unblinding	Figure 3 of study analyses and the footnote is revised.	To update information about unblinding.
5.1.11 Study-specific criteria for interruption / premature discontinuation of study treatment	It is clarified that in case of premature study treatment discontinuation due to interruptions exceeding 14 consecutive days (or 28 consecutive doses if bid regimen or 14 consecutive doses if qd regimen), the premature End-of-	Clarified as in that case the instructions in section 7.1 to perform EDBT/EOLT visit no later than 7 days after the last dose of study treatment is not applicable.

	Double-Blind-Treatment/ End-of-Open-Label-Treatment (EDBT/EOLT) visit must occur within 7 days of the discontinuation criteria being met.	
5.1.12 Treatment of overdose	Information regarding treatment in case of selexipag overdose is included.	To be consistent with Janssen protocol template and processes.
Synopsis; 6.1.2 Secondary efficacy endpoints; 10.2.2 Secondary efficacy variables	Definition of 'Time to clinical worsening (TTCW)' was rephrased.	Editorial clarification.
6.1.3 Other efficacy endpoints;	Information about efficacy endpoints being captured by actigraphy assessment is updated.	Actigraphy endpoints are not yet established for pulmonary hypertension (PH) subjects. Additional evaluations are being conducted in another study.
7.2.3.5 Daily life physical activity (DLPA); 10.2.3 Other efficacy variables	Information about actigraphy raw data to be derived by vendor as per Data Transfer Agreement is updated.	
Table 5 Visit and assessment schedule for subjects entering the PTOP	Post-treatment observation period-end of study (PTOP-EOS) visit timing is corrected.	PTOP-EOS is not applicable for premature EDBT visit. Inconsistency from protocol amendment 2 (version 3) corrected.
7.2.6.1 PAH-SYMPACT® questionnaire	Pulmonary arterial hypertension Symptoms and Impact® Questionnaire (PAH-SYMPACT®) mobile device returning time is updated as Week 52 / Visit 7 (earlier Week 39/Visit 6)	To update the information as per new revised study duration.
9.1.1 Definition of adverse events	Statement related to AEs associated with overdose and study treatment error was deleted.	Captured under Section 9.5 to follow Janssen template
9.2.5 Reporting procedures	Information about reporting procedures for serious adverse events (SAEs) and product quality complaint (PQC) is updated.	To be consistent with Janssen protocol template and processes.
9.3.1 Reporting of pregnancy; 9.3.2 Follow-up of pregnancy	Information about reporting and follow-up procedures for pregnancy is updated.	
9.4 Product quality complaints	A new section is included to define product quality complaints and the procedure for reporting.	
9.5 Special reporting situations	A new section is included to define special reporting situations.	
10.1.7 Usage of the analysis sets	Footnote of Table 6 is revised.	Editorial clarification.

10.2.1 Primary efficacy variable; 10.3.2.2 Handling of missing data	Information about use of left ventricular end diastolic pressure (LVEDP) for pulmonary vascular resistance (PVR) calculation in absence of pulmonary artery wedge pressure (PAWP) measurement is updated.	To clarify that if the PAWP measurement is not available, then LVEDP will be used in the calculation of PVR.
Synopsis; 10.3.1 Overall testing strategy; 10.3.3 Analysis of secondary efficacy variable(s); 10.4 Interim analysis	Testing strategy in Section 10.3.1 for secondary endpoints is changed; a new Table 7 of analysis time points of the primary and secondary efficacy endpoints for double-blind treatment period is included; Figure 4 is revised; the analyses in Sections 10.3.3 and 10.4 are revised accordingly; all these changes have been aligned in Synopsis as well.	To allow declaring success if either 6-minute walk distance (6MWD) or TTCW is statistically significant
Synopsis; 10.3.1 Overall testing strategy; 13 References	New reference in context to weighted Bonferroni-Holm method [Holm 1979].is included and updated in reference list as well.	To support the use of employed statistical method.
Synopsis; 5.1.6.1 Timing of study analyses; 10.4 Interim analysis	Figure 5 (Flow of decision making) and description of analysis time points are revised.	To align with change in testing strategy.
Synopsis; 10.3.5 Subgroup analyses	Predefined subgroup analyses based on race were removed from the protocol.	To allow definition of the subgroup in the statistical analysis plan (SAP) based on race depending on the number within each race category
10.6.3 Time to clinical worsening (according to the CHMP definition)	• Two-sided type I error is revised to 2.5%. • Event number is revised to 148. • Number of months to observe 148 events after the randomization of the last subject is updated to 17 months. • Minor changes made to improve the clarity of the matter.	Updated according to the new testing strategy
13 References	References are updated.	To align with Janssen style guide.
14.10 Appendix 10: Child-Pugh classification; 13 References	The Child-Pugh classification is included, and the corresponding reference is updated.	To provide detailed information for the assessment of severity of liver diseases.
Throughout the protocol	• Independent statistical analysis center (ISAC) is replaced with	To improve the clarity of subject matter; to align with

	Statistical support group (SSG). • Right heart failure related symptoms-worsening is included in TTCW efficacy endpoint. • The term 'Global Drug Safety Department' is deleted. • Minor grammatical, formatting, spelling and abbreviation-related changes are made.	Janssen terminology.

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
6MWT	6-minute walk test
AC	Adjudication committees
AE	Adverse event
ANCOVA	Analysis of covariance
BDI	Borg dyspnea index
bid	Twice daily
Borg CR10®	Borg category-ratio 10 Scale®
BPA	Balloon pulmonary angioplasty
CAC	Central Adjudication Committee
CEC	Clinical Event Committee
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CHMP	Committee for medicinal products for human use
CI	Cardiac index
CL	Confidence limits
CO	Cardiac output
CRO	Contract Research Organization
CSAC	Country-specific Adjudication Committee
CSR	Clinical Study Report
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiogram
CTT	Clinical Trial Team
CYP2C8	Cytochrome P-450 2C8
DB	Double-blind
DLPA	Daily life physical activity
dPAP	Diastolic pulmonary artery pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EDBT	End-of-Double-Blind-Treatment
EOLT	End-of-Open-Label-Treatment
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	Euro Quality of life-5-Dimension-5-Level
ERA	Endothelin receptor antagonist
EU	European Union
FAS	Full Analysis Set
FC	Functional class
FWER	Family-wise error rate
GCP	Good Clinical Practice
HC	Heart catheterization
HES	Hemodynamic set
HR	Heart rate
HSD	Hwang, Shih and DeCani's
IA	Interim analysis
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
iMTD	Individual maximum tolerated dose
IP receptor	Prostacyclin receptor
IRB	Institutional review board
IRT	Interactive Response Technology
ISF	Investigator Site File
LHC	Left Heart Catheterization
LVEDP	Left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary artery pressure

mPAWP	Mean pulmonary arterial wedge pressure
mRAP	Mean right atrial pressure
MRA	Magnetic resonance angiography
NT-proBNP	N-terminal pro b-type natriuretic peptide
OF	O'Brien and Fleming
OL	Open label
PA	Pulmonary angiography
PAH	Pulmonary arterial hypertension
PAH-SYMPACT®	Pulmonary Arterial Hypertension Symptoms and Impact® Questionnaire
PAWP	Pulmonary artery wedge pressure
PDE-5	Phosphodiesterase type-5
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PI	Principal Investigator
PPS	Per-protocol Analysis Set
PPS1	PVR Per-protocol Analysis Set
PPS2	6MWD Per-protocol Analysis Set
PQC	Product quality complaint
PRO	Patient-reported outcome
PTOP	Post-treatment observation period
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
qd	Once daily
QS	Quality System
RHC	Right heart catheterization
RSI	Reference safety information
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan

SBP	Systolic blood pressure
SC	Steering Committee
SD	Standard deviation
SDO	Secure data office
SFU	Safety follow-up
sGC	Soluble guanylate cyclase
SI	International System of Units
SIV	Site initiation visit
SM	Site manager
SOC	System organ class
sPAP	Systolic pulmonary artery pressure
SSG	Statistical Support Group
SUSAR	Suspected unexpected serious adverse reaction
SvO_2	Mixed venous oxygen saturation
T3	Tri-iodothyronine
T4	Thyroxin
TSH	Thyroid stimulating hormone
TST	Total sleep time
TTCW	Time to clinical worsening
US	United States
V/Q	Ventilation/perfusion
WASO	Wake after sleep onset
WHO	World Health Organization
WPAI©: GH	Work Productivity and Activity Impairment: General Health

PROTOCOL SYNOPSIS AC-065B302

TITLE	A multicenter, randomized, double-blind, placebo-controlled, parallel-group, group-sequential, adaptive, Phase 3 study with open-label extension period to assess the efficacy and safety of selexipag as an add-on to standard of care therapy in subjects with inoperable or persistent/recurrent after surgical and/or interventional treatment Chronic Thromboembolic Pulmonary Hypertension (CTEPH).
ACRONYM	SELECT **SELE**xipag in inoperable or persistent/recurrent **C**hronic **T**hromboembolic pulmonary hypertension
OBJECTIVES	**Primary objective(s)** To evaluate the effect of selexipag on pulmonary vascular resistance (PVR) versus placebo in subjects with inoperable CTEPH (ie, technically non-operable) and persistent/recurrent CTEPH after surgical (pulmonary endarterectomy [PEA]) and/or interventional (balloon pulmonary angioplasty [BPA]) treatment at Week 20. **Secondary objectives** To evaluate the effects of selexipag versus placebo on: • Exercise capacity. • Time to clinical worsening (TTCW). • All-cause death or hospitalizations related to Pulmonary Hypertension (PH) worsening. • World Health Organization (WHO) functional class (FC). • Patient-reported outcomes. • Dyspnea. • N-terminal pro b-type natriuretic peptide (NT-proBNP). **Other objectives** Other objectives are described in Sections 2.3 and 2.4.
DESIGN	A prospective, multicenter, randomized, double-blind, placebo-controlled, add-on to standard of care, parallel-group, group-sequential, adaptive Phase 3 study with an open-label extension period.

	Up to 280 subjects will be randomized in a 1:1 ratio to receive either selexipag or placebo during the double blind (DB) period. Subjects completing the DB period will enter the open-label extension period and will receive selexipag. Subjects will be recruited in two sequential cohorts. Approximately the first 90 randomized subjects will constitute the hemodynamic cohort who, in addition to the overall study assessments, will undergo an right heart catheterization (RHC) (and left heart catheterization [LHC], if needed) at Week 20. The remaining subjects will constitute the non-hemodynamic cohort who do not require a post-baseline hemodynamic assessment. Both cohorts are combined for the evaluation of secondary efficacy endpoints. Treatment allocation will be stratified by: • Treatment with PH-specific therapies (ie, endothelin receptor antagonists [ERAs], phosphodiesterase type-5 inhibitor (PDE-5i), soluble guanylate cyclase stimulator [riociguat]; one versus two versus naive [naive capped at 40%]) and • CTEPH population (inoperable [with or without BPA] versus persistent/recurrent after PEA [including PEA followed by BPA]). The database will be locked and analyzed at five time points during the study: • Time point 1: when approximately 90 randomized subjects, the hemodynamic cohort, have completed the Week 20 RHC (and LHC, if needed) or prematurely discontinued from the study, the final analysis for the PVR endpoint will be performed by an independent Statistical Support Group (SSG) for the Independent Data Monitoring Committee (IDMC). • Time point 2: when approximately 160 randomized subjects have completed the Week 26 6-minute walk distance (6MWD) assessment or prematurely discontinued from the study, an interim analysis (IA) for the 6MWD

	endpoint and the TTCW endpoint will be performed by the independent SSG for the IDMC. • Time point 3: when all (up to 280) randomized subjects have completed the Week 26 6MWD assessment or prematurely discontinued from the study, the final analysis for the 6MWD endpoint and an IA for the TTCW endpoint will be performed by the independent SSG for the IDMC. • Time point 4: when all (up to 280) randomized subjects have completed the DB treatment period or the post-treatment observation period (PTOP) or prematurely discontinued from the study, the DB database will be locked, the data extract will be performed and unblinding will occur. The final analysis for all endpoints will be performed by the sponsor. • Time point 5: when all (up to 280) randomized subjects have performed their End-of-Study (EOS) visit, an analysis including OL period data will be performed by the sponsor.
PERIODS	**Screening period:** Lasts at least 14 days and up to 60 days; starts with the signature of the informed consent and ends with the subject's randomization at Visit 2, Day 1. **Double-blind treatment period:** Starts with the administration of the first dose of DB study treatment in the evening of the day of randomization (Visit 2) (except in case of once daily [qd] dosing, where the subjects must take the study treatment in the morning) and with a titration phase of up to 12 weeks. It ends on the day of the last dose of DB study treatment with the End-of-Double-Blind-Treatment (EDBT) visit. The EDBT visit will occur shortly (within 4 weeks) after the announcement of end-of-double-blind period, for all subjects who have not discontinued study treatment prematurely. The end-of-double-blind period will be announced by the sponsor when the overall target number of clinical worsening events has been reached [see Section 10.6.3], or earlier following recommendation of the IDMC [see Section 10.4] or sponsor's decision [see Section 8.3]. **Open-label treatment extension period:** For subjects who completed the DB treatment period, the OL treatment

	extension period will last at least until the DB period results release and up to a maximum of 26 weeks after the DB period results release. It starts with the first dose of the OL study treatment in the evening of the day of the last dose of DB study treatment, ie, the EDBT visit (except in case of qd dosing, where the subjects must take the study treatment in the morning). All subjects will have a titration phase of up to 12 weeks. It ends with the End-of-Open-Label-Treatment (EOLT) visit that occurs any time within 26 weeks of the DB period results release. **Follow-up period:** Starts on the day after the last dose of OL study treatment and ends 30–35 days thereafter with the safety follow-up telephone call. **Post-treatment observation period:** Subjects who prematurely discontinue the DB treatment period will enter a PTOP and will continue to perform the visits and assessments as scheduled until the PTOP-EOS visit [see Section 5.1.10], provided the subject's consent for this limited participation in the study has not been withdrawn [see Section 8.2].
PLANNED DURATION	The maximum duration of participation of a subject in the study will be approximately 74 months.
SITE(S) / COUNTRY(IES)	Approximately 195 sites in 40 countries (planned).
SUBJECTS / GROUPS	Up to 280 subjects in two groups; randomized in a 1:1 ratio to receive either selexipag or placebo during the DB period. Subjects will be recruited in two sequential cohorts. Approximately the first 90 randomized subjects will constitute the hemodynamic cohort and, in addition to the overall study assessments, will undergo an RHC (and LHC, if needed) at Week 20 [see Section 7.2.3.1.2]. The remaining subjects will constitute the non-hemodynamic cohort.
INCLUSION CRITERIA	1. Signed and dated Informed Consent Form. 2. Male and female subjects ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤85 years old at Screening (Visit 1).

	3. Subjects with diagnosis of CTEPH and inoperability confirmed by the corresponding Adjudication Committee (AC; Country-specific Adjudication Committee [CSAC] or Central Adjudication Committee [CAC]) [see Section 3.4.3], defined as one of the following options: a. Inoperable CTEPH (ie, technically non-operable) with: – Diagnosis of CTEPH based on at least two of the following assessments performed in the 14-month period prior to randomization (Visit 2): o ventilation/perfusion (V/Q) scan, o pulmonary angiography (PA), o computed tomography pulmonary angiogram (CTPA), and/or o magnetic resonance angiography (MRA). – RHC (and LHC, if needed) [1] performed at least 90 days after start of full anticoagulation, showing: o PVR at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units for the hemodynamic cohort and PVR at rest ≥300 dyn.sec/cm^5 or ≥3.75 Wood units for the non-hemodynamic cohort, o Mean pulmonary arterial pressure (mPAP) ≥25 mmHg, o Pulmonary arterial wedge pressure (PAWP) ≤15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) ≤15 mmHg. b. Persistent/recurrent CTEPH after BPA, and deemed inoperable with: – Diagnosis of CTEPH based on at least one of the following assessments performed in the 14-month period prior to randomization (Visit 2) and after last interventional (BPA) treatment: ventilation/perfusion (V/Q) scan, PA, CTPA or MRA. – RHC (and LHC, if needed)[1] performed at least 90 days after last interventional (BPA) treatment and at least 90 days after start of full anticoagulation, showing:

	○ PVR at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units for the hemodynamic cohort and PVR at rest ≥300 dyn.sec/cm^5 or ≥3.75 Wood units for the non-hemodynamic cohort, ○ mPAP ≥25 mmHg, ○ PAWP ≤15 mmHg, or, if not available or unreliable, an LVEDP ≤15 mmHg. c. Persistent/recurrent CTEPH after PEA (including PEA followed by BPA) with: – Diagnosis of CTEPH based on at least one of the following assessments performed in the 14-month period prior to randomization (Visit 2) and after last surgical (PEA) or interventional (BPA) treatment: V/Q scan, PA, CTPA or MRA. – RHC (and LHC, if needed)[1] performed at least 90 days after last surgical (PEA) or interventional (BPA) treatment and at least 90 days after start of full anticoagulation, showing: ○ PVR at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units for the hemodynamic cohort and PVR at rest ≥300 dyn.sec/cm^5 or ≥3.75 Wood units for the non-hemodynamic cohort, ○ mPAP ≥25 mmHg, ○ PAWP ≤15 mmHg, or, if not available or unreliable, an LVEDP ≤15 mmHg. 4. PH in WHO FC I–IV. 5. Subject able to perform the 6MWT with a minimum distance of 100 m and a maximum distance of 450 m at Screening Visit (Visit 1). 6. A woman of childbearing potential [see definition in Section 4.5.1] is eligible only if all the following applies: a. Negative serum pregnancy test at Screening and a negative urine pregnancy test at randomization. b. Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation. c. Agreement to use one of the methods of birth control described in Section 4.5 from Screening visit up to at least 30 days after study treatment discontinuation.

	[1] For the hemodynamic cohort, a historical RHC/LHC is allowed, provided it was performed within 30 days prior to Screening*, at least 90 days after last change in PH-specific therapies (ie, change in dose or initiation of new class of drugs) and as per guidance in Appendix 1. For the non-hemodynamic cohort, a historical RHC is allowed, provided it was performed within 6 months prior to Screening*. * In case of rescreening in the hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC, if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit. In case of rescreening in the non-hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used. If no historical results are available, an RHC (and LHC, if needed) must be performed during the Screening period (as per guidance in Appendix 1 for the hemodynamic cohort).
EXCLUSION CRITERIA	**Exclusion criteria related to the disease** 1. Planned BPA within 26 weeks after randomization. 2. Change in dose or initiation of new PH-specific therapy within 90 days prior to the baseline RHC (and LHC, if needed) qualifying for enrollment for the hemodynamic cohort and within 90 days prior to randomization (Visit 2) for the non-hemodynamic cohort. 3. Treatment with prostacyclin (epoprostenol), prostacyclin analogs (ie, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/Uptravi) within 90 days prior to randomization (Visit 2), except those given at vasodilator testing during RHC. 4. Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to baseline RHC (and LHC, if needed). **Exclusion criteria related to comorbidities** 5. Severe coronary heart disease or unstable angina as assessed by the investigator. 6. Myocardial infarction within the last 6 months prior to or during Screening. 7. Decompensated cardiac failure if not under close supervision.

	8. Severe arrhythmias as assessed by the investigator. 9. Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months prior to or during screening. 10. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH. 11. Known or suspicion of pulmonary veno-occlusive disease. **Exclusion criteria related to selexipag use** 12. Known and documented severe hepatic impairment, eg, Child-Pugh Class C[2]. 13. Severe renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2 or serum creatinine >2.5 mg/dL or 221 μmol/L) at Screening. 14. Known or suspected uncontrolled thyroid disease as per investigator judgment. 15. Pregnant, planning to be become pregnant or lactating. 16. Treatment with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; eg, gemfibrozil) or moderate inducers of CYP2C8 (eg, rifampicin) within 14 days prior to randomization. 17. Systolic blood pressure <90 mmHg at Screening (Visit 1) or at randomization (Visit 2). 18. Known hypersensitivity to selexipag or drugs of the same class, or any of their excipients. **General exclusion criteria** 19. Planned or current treatment with another investigational treatment up to 3 months prior to randomization. 20. Any co-morbid condition that may influence the ability to perform a reliable and reproducible 6MWT, including use of walking aids (cane, walker, etc.). 21. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence or psychiatric disease. 22. Known concomitant life-threatening disease with a life expectancy <12 months.

	[2] The assessment of hepatic impairment (Child-Pugh Score as per Appendix 10) must be fully documented for patients who have clinical signs and evidence (from central and/or local lab) of hepatic impairment.
STUDY TREATMENTS	**Investigational treatment** DB and OL selexipag 200 µg, oral tablets in childproof bottles, up-titrated to allow each subject to reach their individual maximum tolerated dose (iMTD), in the range of 200 µg to 1600 µg. Dosing frequency will be twice daily (bid), with an interval of approximately 12 hours. For subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide), the dosing frequency is once daily (qd) [see Section 5.1.9]. The DB study treatment refers to either DB selexipag 200 µg or the matching placebo, administered during the DB treatment period. The OL study treatment refers to OL selexipag 200 µg, administered during the OL period. If not otherwise specified, study treatment refers to both DB and open-label study treatments. Depending on the iMTD, a single dose of study treatment will consist of 1–8 tablets (200–1600 µg). **Comparator and/or placebo** Matching placebo, bid or qd.
AUXILIARY MEDICINAL PRODUCTS	All subjects must receive full anticoagulation treatment, as per local practice, from 90 days prior to the baseline RHC (and LHC, if needed) assessment and up to EOS.
ENDPOINTS	**Primary efficacy endpoint** PVR at Week 20, assessed at rest, within 2–5 hours post-dose, expressed as a percent of baseline PVR. **Secondary efficacy endpoints** • Change from baseline in 6MWD to Week 26 (key secondary endpoint). • Time to clinical worsening (key secondary endpoint), where clinical worsening is defined (adapted from the

	Committee for medicinal products for human use [CHMP] definition [EMEA 2008]) as at least one of the following components, confirmed by the clinical event committee (CEC), when applicable: o All-cause death o Non-planned PH-related hospitalization o PH-related deterioration identified by at least one of the following: o Increase from baseline in WHO FC[3]; o Deterioration from baseline by at least 15% in exercise capacity as measured by the 6MWD[3]; o New or worsening of signs or symptoms of right heart failure defined as a reported adverse event (AE) with one of the following preferred terms: "CTEPH", "pulmonary hypertension", "right ventricular failure", "right ventricular dysfunction" and "acute right ventricular failure". • All-cause death or hospitalizations related to PH worsening. • Improvement in WHO FC from baseline to Week 26. • Change from baseline to Week 26 in Pulmonary arterial hypertension symptoms and impact questionnaire (PAH-SYMPACT®) cardiopulmonary symptoms domain and cardiovascular symptoms domain. • Change from baseline to Week 26 in the Borg dyspnea index/Borg CR10®. • Change from baseline to Week 26 in NT-proBNP. [3] Confirmed by a second measurement performed on a different day within 14 days **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Safety endpoints** • Treatment-emergent AEs [5] up to 3 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].

	• Serious adverse events (SAEs) up to 30 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1]. • AEs leading to premature discontinuation of study treatment at each analysis time point [see Section 5.1.6.1]. • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points during the study at each analysis time point [see Section 5.1.6.1]. • Treatment-emergent marked laboratory abnormalities up to 3 days after study treatment discontinuation, as detailed in Appendix 2, at each analysis time point [see Section 5.1.6.1]. • Treatment-emergent AEs[5] of special interest (eg, hypotension, anemia, hyperthyroidism) up to 3 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1]. [5] A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment start until 3 days after study treatment discontinuation), whether or not considered by the investigator as related to study treatment.
ASSESSMENTS	Refer to the schedule of assessments in Table 3, Table 4 and Table 5.
STATISTICAL METHODOLOGY	There will be up to five analysis time points: At analysis time point 1, the analysis of the primary efficacy endpoint PVR will be conducted on the Hemodynamic Set (HES). If the analysis of PVR is statistically significant, the study will proceed as planned; otherwise, the study will be terminated. The IDMC will review the results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC. At analysis time point 2, unblinded IA for 6MWD and TTCW will be conducted on the Full Analysis Set (FAS). If both 6MWD and TTCW are futile, then the study will be terminated prematurely. If at least one of 6MWD and TTCW is statistically significant, the study will be terminated due to

	overwhelming efficacy and subject recruitment will be stopped, but subjects already enrolled will remain on DB treatment as planned until all subjects have completed Week 26 assessments or prematurely discontinued from the study. Otherwise, the study will proceed as planned. The IDMC will review the results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC. At analysis time point 3, an unblinded final analysis for 6MWD and an unblinded IA for TTCW will be conducted on the FAS. If 6MWD is not statistically significant and TTCW is futile, then the study will be terminated prematurely. If at least one of 6MWD and TTCW is statistically significant, the study will be terminated due to overwhelming efficacy. Otherwise, the study will proceed as planned. The IDMC will review the results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC. At analysis time point 4, the DB database will be locked, the data extract will be performed and unblinding will occur. This final analysis of the DB treatment period will be conducted by the sponsor. At analysis time point 5, the data from all subjects enrolled in the OL treatment extension period will be summarized and reported. The analysis at this time point will be considered the final analysis of the study and will correspond to the completion of the OL treatment extension period. **Primary efficacy variable** The primary efficacy variable is the percent of baseline PVR at Week 20, defined as: (PVR (dyn.sec/cm^5) at Week 20 / PVR (dyn.sec/cm^5) at baseline) × 100 The hypotheses for the primary endpoint are formulated in terms of geometric mean of percent of baseline PVR at Week 20 in subjects treated with selexipag versus placebo:

	H_0: $GM_{selexipag} = GM_{placebo}$ H_A: $GM_{selexipag} \neq GM_{placebo}$ where: $GM_{selexipag}$ and $GM_{placebo}$ are the geometric means of percent of baseline PVR at Week 20 for subjects treated with selexipag and placebo, respectively. The null hypothesis for the primary efficacy variable will be tested on the hemodynamic cohort by means of an analysis of covariance (ANCOVA) model on the $\log_e$ transformed percent of baseline PVR at Week 20 (including imputed values). Model covariates will include randomized treatment, stratification factors (PH-specific therapies and CTEPH population), and the $\log_e$-transformed baseline PVR value. The resulting arithmetic mean and 95% confidence limits (CL) of the natural logarithm of the ratio: PVR at Week 20 / PVR at baseline will be inversely transformed using the exponential function and multiplied by 100 to provide the geometric mean of the ratio and corresponding 95% CL, expressed as a percent, by treatment group. Imputation methods for the primary endpoint, PVR at Week 20, are described in Section 10.3.2.2. At analysis time point 1 the primary endpoint PVR will be tested in the hemodynamic cohort at full two-sided alpha of 5%. Failure to meet success on the primary endpoint in this analysis will lead to termination of the study for futility, as no remaining alpha is available to test secondary endpoints. **Key secondary variables** There are two key secondary variables, 6MWD and TTCW. To allow for the declaration of study success if the test of at least either 6MWD or TTCW reaches statistical significance, a graphical testing strategy based on weighted Bonferroni-Holm method [Holm 1979; Bretz 2009] will be implemented, controlling the family-wise error rate (FWER) at a two-sided significance level of α=5% for the primary and secondary

	efficacy variables. The significance level is initially split equally to 6MWD and TTCW. The 6MWD efficacy variable is the change from baseline to Week 26 in 6MWD (in meters) as defined by: (6MWD [m] at Week 26 − 6MWD [m] at baseline). The null hypothesis is that there is no difference between selexipag and placebo for change from baseline to Week 26 in 6MWD. The analysis will be an ANCOVA (with baseline 6MWD, all stratification factors, treatment group as covariates). Least squares estimates for each treatment group and for the placebo-corrected treatment effect will be displayed. This endpoint will be tested at analysis time points 2 and 3 on the FAS. To preserve the type I error rate, the Hwang, Shih and DeCani's error spending function with parameter γ=−4 [Hwang 1990] will be applied. The alpha to be spent in the IA depends on the fraction of available information on 6MWD at time of the IA. The TTCW efficacy variable (according to the CHMP definition) is calculated from date of randomization to the date of onset of the first component event. The null hypothesis is that there is no difference between selexipag and placebo for the distribution of time to the first CHMP-defined clinical worsening event. A two-sided stratified (for the stratification factors) log-rank test will be applied. Kaplan-Meier point and interval estimates for the survival functions will be provided. The hazard ratio will be estimated using a Cox model, including treatment group and all stratification factors as covariates. This endpoint will be tested at analysis time points 2, 3 and 4 on the FAS. To preserve the type I error rate, the O'Brien and Fleming-type error spending function will be applied [Lan 1983]. The alpha to be spent in the IA depends on the fraction of available information on TTCW at time of the IA. **Safety variables**

	Safety variables: treatment-emergent AEs, SAEs, AEs leading to permanent discontinuation of study treatment, treatment-emergent AEs of special interest, reasons for premature discontinuation of study treatment, number of and reason for deaths, changes in vital signs and treatment-emergent marked laboratory abnormalities will be listed and summarized by frequency tables. **Subgroup analyses** Subgroup analyses will be conducted to assess results consistency on the primary endpoint and on selected secondary endpoints, based on the following baseline characteristics: • Stratification factor 1: PH-specific therapies (one versus two versus naive); • Stratification factor 2: CTEPH population (inoperable [with or without BPA] versus persistent-recurrent after PEA [including PEA followed by BPA]); • Participation in the hemodynamic cohort; • Gender; • Race (as defined in the statistical analysis plan [SAP]); • Geographic region (as defined in the SAP). An additional subgroup analysis on the primary endpoint and on selected secondary endpoints will be conducted by dose group (low [200–400 µg bid], medium [600, 800 and 1000 µg bid] and high [1200, 1400 and 1600 µg bid]). **Sample size** Up to 280 subjects are planned to be randomized in this study. The study will consist of two cohorts: approximately the first 90 subjects will be randomized in the hemodynamic cohort, targeting the primary endpoint of PVR. The remaining subjects will be randomized to enrich information on all secondary endpoints.

	A sample size of 90 subjects will provide a power of >90% at two-sided alpha 5% for the primary endpoint (PVR) under the assumed effect of a 30% relative improvement in geometric mean as compared to placebo at Week 20 and a coefficient of variation of 35–50%. The sample size of 280 subjects will provide a power of 90% at two-sided alpha 2.5% for the key secondary endpoint 6MWD under the assumed effect of a 34 m difference in 6MWD at a standard deviation of 80 m with one IA, and a power of 80% at two-sided alpha 2.5% for the key secondary endpoint TTCW under the assumed hazard ratio of 0.6, a no-event rate of 0.7 at 12 months in the placebo arm and a total of 148 events, with two IAs. [Section 10.6].
STUDY COMMITTEES	A Steering Committee has been appointed by the sponsor to contribute to the design of the protocol, oversee the conduct of the study, evaluate the results and support publications. An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is conducted with the highest scientific and ethical standards. It will interpret the results of the planned analyses at analysis time points 1, 2, and 3. The IDMC will be fully operational prior to enrollment of the first subject into the study. Two sets of independent ACs are established to confirm the inoperability and the persistence/recurrence of PH of CTEPH subjects considered eligible for study inclusion by the investigational sites: • CSAC and • CAC for countries without a CSAC. These committees will review predefined data for each subject and assess whether CTEPH diagnosis and persistence/recurrence of PH (when applicable) are confirmed and the inoperability criterion is met prior to randomization. In addition, the ACs will confirm the scientific and medical

	plausibility of all Week 20 hemodynamic parameters as compared to the baseline values. **Clinical Event Committee** A CEC has been appointed by the sponsor to adjudicate, in a blinded fashion, components of the clinical worsening events.

PROTOCOL

1 BACKGROUND

1.1 Indication

Pulmonary hypertension (PH) is a rare pathophysiological disorder that may involve multiple clinical conditions and can complicate several cardiovascular and respiratory diseases such as left ventricular dysfunction and chronic obstructive pulmonary disease.

Chronic thromboembolic pulmonary hypertension (CTEPH) most commonly develops from the obstruction of pulmonary artery branches following episodes of acute or recurrent pulmonary embolism (PE) with incomplete thrombus resolution, formation of fibrosis and remodeling of pulmonary blood vessels. Based on the European CTEPH registry, a large contemporary, international, prospective registry that included 679 newly diagnosed CTEPH patients, the majority of patients evaluated for CTEPH had been previously diagnosed with acute PE. Specifically, a history of deep venous thrombosis and acute PE was observed in 56% and 75%, respectively, of patients with CTEPH in this registry [Pepke-Zaba 2011].

CTEPH is one of the leading causes of severe PH, categorized by the World Health Organization (WHO) and the Nice Classification as Group 4 [Galiè 2016]. CTEPH is defined as precapillary PH (resting mean pulmonary arterial pressure [mPAP] ≥25 mmHg, mean pulmonary arterial wedge pressure [mPAWP] ≤ 15 mmHg) in the presence of non-resolving organized thromboemboli that are located proximally or more distally in the pulmonary arterial tree (main, lobar, segmental, subsegmental pulmonary arteries) and that persist at least 3 months after the onset of anticoagulant therapy [Gopalan 2016]. The arteriopathy observed in CTEPH has a histopathology indistinguishable from that observed in pulmonary arterial hypertension (PAH) and affects vascular territories beyond those affected by unresolved thromboemboli.

Pulmonary endarterectomy (PEA) surgery is the treatment of choice for patients with symptomatic, operable CTEPH, which means CTEPH is a potentially curable form of PH. However, if left untreated, because it is unrecognized or inoperable, CTEPH leads to progressively increasing pulmonary vascular resistance (PVR) and eventually right ventricle failure and death [Jenkins 2013]. Balloon pulmonary angioplasty (BPA) is an emerging therapeutic option for patients diagnosed with inoperable CTEPH that is currently being assessed for the treatment of CTEPH, as it is likely to address changes in medium- to small-sized pulmonary arteries[Galiè 2016].

PVR represents a relevant assessment in CTEPH with direct implications for patient management, given that baseline values have been shown to be linked to outcome. A high

PVR (>584 dyn.sec/cm^5) and a high mPAP (>40 mmHg) are prognostic for increased mortality [Saouti 2009].

1.2 Study treatment(s)

Selexipag (ACT-293987) is an orally available, selective and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor) approved and commercially available for the treatment of patients with PAH in the US, EU, Japan and other countries.

Selexipag is currently under development in Japan for CTEPH and arteriosclerosis obliterans with intermittent claudication.

For detailed information, refer to the Investigator's Brochure [Selexipag IB].

1.3 Purpose and rationale of the study

This study will be the first global, randomized, controlled study to explore the efficacy and safety of an oral IP-receptor agonist in an inoperable or persistent/recurrent CTEPH population treated with standard of care and, as such, will address the role of the oral IP-receptor agonist selexipag in a first-line and add-on setting. The purpose of this study is to obtain registration of selexipag in the studied indication and population.

This study assesses important data intended to guide clinical decision making and support the filing for regulatory approval, including but not limited to hemodynamics, 6-minute walk distance (6MWD) and clinical worsening.

The rationale for this study rests in the observed efficacy of PH-specific therapies such as riociguat and macitentan in inoperable and persistent/recurrent CTEPH. This is further supported by shared histopathologic findings including endothelial cell dysfunction and distal pulmonary arterial remodeling between PAH and CTEPH [Humbert 2010].

Selexipag Phase 2 study in CTEPH

Study AC-065B201 was a Phase 2 study conducted in Japanese patients with inoperable and/or persistent/recurrent CTEPH. A total of 34 patients were enrolled in this study and assigned to treatment with placebo or selexipag with a ratio of 1:3. Patients were treated following an up-titration regimen, based on the tolerability of each subject, starting at a dose of 100 µg twice daily (bid) up to a maximum dose of 800 µg bid. Concomitant use of either an endothelin receptor antagonist (ERA) or a phosphodiesterase type-5 (PDE-5) inhibitor was allowed in this study. In the Per-protocol Set (N=28), selexipag treatment was associated with a mean change from baseline to Week 17 in PVR of −104 dyn.sec/cm^5 (95% confidence limits [CL]: −191 and −17 dyn.sec/cm^5) compared to an increase of 26 dyn.sec/cm^5 in the placebo group (95% CL: −140 and 192 dyn.sec/cm^5). The treatment effect in percentage change from baseline to Week 17 in PVR over placebo with selexipag

was −16.3% (95% CL: −34.7 and 7.3%), with p-values of 0.1553 (Wilcoxon rank sum test) and 0.1260 (t-test). No effect on 6MWD was observed (−9 m, 95% CL=−57 to 39 m). The interpretability of this study is considered limited, given the cap on the maximal permitted dose at half of the currently approved maximum selexipag dose in PAH, which suggests that not all patients were on their individual maximal tolerated, and thus effective, dose. A *post-hoc* analysis in patients with and without notable prostacyclin-associated adverse events (AEs) suggested improved efficacy on both hemodynamic and exercise capacity parameters in patients who experienced prostacyclin-associated AEs (data on file).

The data from study AC-065B201 support the current design despite the lack of an effect on 6MWD, given the observed hemodynamic effects in a study in which a potentially sub-maximal dose was given and in view of the observed treatment effect in patients who have likely reached their individual maximum tolerated dose (iMTD), as evidenced by the occurrence of relevant prostacyclin-associated AEs.

1.4 Summary of known benefits and potential risks

1.4.1 Benefits

Selexipag, a non-prostanoid IP-receptor agonist, is an orally available medicine with pharmacokinetic characteristics suitable for bid dosing.

Efficacy of selexipag in the treatment of adult patients with symptomatic PAH was demonstrated in the AC-065A302 (GRIPHON) study, the largest (N=1156) and only randomized long-term (mean duration 1.5 years and up to 4.2 years), controlled morbidity/mortality study conducted with an IP-receptor agonist [Sitbon 2015]. A highly statistically significant effect on the primary endpoint, risk of first morbidity or mortality event during treatment, was observed: the hazard ratio versus placebo was 0.60 (99% CL: 0.46, 0.78; 1-sided unstratified log-rank p=0.0001), corresponding to a 40% relative risk reduction versus placebo. The treatment effect was consistent across WHO functional class (FC) II–III and was fully preserved in patients already treated with an approved PAH-specific medicine at baseline (80% of the study population), as well as in patients treated with two such medicines (30% of the study population). In all analyses, the effect of selexipag was established early and was sustained over this long-term study, in which the median duration of treatment was nearly 1.5 years. GRIPHON was the first study to demonstrate the long-term outcome benefit of an IP-receptor agonist, in particular when added sequentially to therapies acting on other pathogenic pathways in PAH (endothelin and nitric oxide pathways). The study outcome is reflected in the current consensus guidelines for PAH, where selexipag is the only IP-receptor agonist with a Class I evidence recommendation for sequential drug combination therapy [Galiè 2016].

Given the pathophysiological and clinical similarities between CTEPH and PAH due to distal pulmonary arteriopathy, as well as the demonstrated efficacy of PAH-targeted therapies in inoperable CTEPH [Ghofrani 2013, Ghofrani 2017], it is believed that CTEPH patients could benefit from selexipag treatment, thus providing an alternate treatment option for these patients.

1.4.2 Possible risks

The tolerability and safety profile of selexipag administered to CTEPH patients is expected to be consistent with that in adult patients with PAH.

The short and long-term safety profile of oral selexipag has been established in PAH patients in the GRIPHON study conducted in 1156 subjects and is mainly characterized by prostacyclin-associated AEs associated with the mode of action of selexipag. Such AEs typically occur during the initial phase of individualized dose titration, and the susceptibility varies between individuals. Adverse reactions, reflecting the mode of action of selexipag, included headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia and flushing.

Hypotension was reported more frequently in the selexipag group than in the placebo group (5.0% and 3.1%, respectively). In the selexipag group, 9.7% of patients had systolic blood pressure (SBP) <90 mmHg on at least one occasion, compared to 6.7% in the placebo group. A decrease from baseline of >40 mmHg in SBP was reported for 2.3% and 3.0% of patients in the selexipag and placebo groups, respectively.

Bleeding was not observed more frequently in selexipag-treated patients compared to placebo, including in those patients treated concomitantly with anticoagulants.

Anemia was reported more frequently in the selexipag group, and a small reduction in hemoglobin was observed at most post-baseline visits.

Hyperthyroidism was reported more frequently in the selexipag group compared to the placebo group. Corresponding laboratory changes were a small reduction in thyroid-stimulating hormone at most post-baseline visits.

The safety profile established in a Phase 2 study of selexipag in inoperable and persistent/recurrent CTEPH, conducted in Japanese patients [see Section 1.3], did not indicate any additional safety risk for selexipag in this indication. The risks associated with study participation beyond those described above for selexipag are limited to those associated with prolonged placebo treatment and those associated with study-specific procedures (eg, repeated blood sampling for safety assessments, right heart catheterization [RHC], etc.).

A potential risk is associated with the re-uptitration of subjects previously randomized to selexipag at the start of the OL study period, potentially resulting in a limited period of lower drug exposure in subjects. This measure is deemed necessary to preserve the blind prior to the analysis of endpoints assessed at the Week 52 time point. This potential risk is deemed low and acceptable given the demonstrated absence of any adverse outcomes following temporary interruption of selexipag treatment in the GRIPHON study [Preston 2018].

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

- External adjudication of eligibility ensuring enrollment of subjects with a potential for benefit from medicinal treatment.
- Exclusion of subjects with unstable PH condition or severe comorbidities [see Section 4.4].
- Allowed changes to PH-specific therapies following the Week 26 visit (new introduction or dose adjustments) and BPA to mitigate any risk associated with prolonged double-blind (DB) treatment.
- Close monitoring of the study by an external Independent Data Monitoring Committee (IDMC) throughout the study.

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

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to evaluate the effect of selexipag on PVR versus placebo in subjects with inoperable CTEPH (ie, technically non-operable) and persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment at Week 20.

2.2 Secondary objectives

The secondary objectives of the study are to evaluate the effects of selexipag versus placebo on:

- Exercise capacity.
- Time to clinical worsening (TTCW).
- All-cause death or hospitalizations related to PH worsening.

- WHO FC.
- Patient-reported outcomes (PROs).
- Dyspnea.
- N-terminal pro b-type natriuretic peptide (NT-proBNP).

2.3 Other efficacy objective

The other objective of the study is to evaluate the effects of selexipag versus placebo on exploratory efficacy assessments.

2.4 Safety objective

The safety objective of the study is to evaluate the safety and tolerability of selexipag versus placebo in subjects with CTEPH.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multicenter, randomized, double-blind, placebo-controlled, add-on to standard of care, parallel-group, group-sequential, adaptive Phase 3 study with an open-label extension period [Figure 1].

Up to 280 subjects will be randomized in a 1:1 ratio to receive either selexipag or placebo during the DB period. Subjects completing the DB period will enter the open-label (OL) extension period and will receive selexipag [see Section 5.1.3.2 for open-label treatment initiation].

Subjects will be recruited in two sequential cohorts. Approximately the first 90 randomized subjects will constitute the hemodynamic cohort and, in addition to the overall study assessments, will undergo an RHC (and left heart catheterization [LHC], if needed) at Week 20 [see Section 7.2.3.1.2]. The remaining subjects will constitute the non-hemodynamic cohort, who do not require a post-baseline hemodynamic assessment. Both cohorts are combined for the evaluation of secondary efficacy endpoints.

Treatment allocation will be stratified by:

- Treatment with PH-specific therapies (ie, ERAs, PDE-5 inhibitors, soluble guanylate cyclase [sGC] stimulators [riociguat]): one versus two versus naive [naive capped at 40%]) and
- CTEPH population: inoperable (with or without BPA) versus persistent/recurrent after PEA (including PEA followed by BPA).

The study will be conducted in approximately 195 sites in 40 countries.

The database will be locked and analyzed at five time points during the study, as described in Section 5.1.6.1. Actions to be taken following these analyses are defined in Section 10.4.

3.1.1 Study periods

The study comprises the following consecutive periods for both cohorts:

3.1.1.1 Screening period

Lasts at least 14 days and up to 60 days; starts with the signature of the informed consent and ends with the subject's randomization at Visit 2, Day 1.

3.1.1.2 Treatment periods

Double-blind treatment period: The DB treatment period starts with the administration of the first dose of DB study treatment in the evening of the day of randomization (Visit 2) (except in case of qd dosing; see Section 5.1.3.1) and with a titration phase of up to 12 weeks. It ends on the day of the last dose of DB study treatment with the End-of-Double-Blind-Treatment (EDBT) visit.

The EDBT visit will occur shortly (within 4 weeks) after the announcement of end-of-double-blind period, for all subjects who have not discontinued study treatment prematurely. The end-of-double-blind period will be announced by the sponsor when the overall target number of clinical worsening events has been reached [see Section 10.6.3], or earlier following recommendation of the IDMC [see Section 10.4] or sponsor's decision [see Section 8.3].

Open-label treatment extension period: For subjects who completed the DB treatment period, the OL treatment extension period will last at least until the DB period results release and up to a maximum of 26 weeks after the DB period results release. It starts with the first dose of the OL study treatment in the evening of the day of the last dose of DB study treatment, ie, the EDBT visit (except in case of qd dosing; see Section 5.1.3.2). All subjects will have a titration phase of up to 12 weeks. It ends with the End-of-Open-Label-Treatment (EOLT) visit that occurs any time within 26 weeks of the DB period results release.

3.1.1.3 Follow-up period

Starts on the day after the last dose of OL study treatment and ends 30–35 days thereafter with the safety follow-up telephone call.

3.1.1.4 Post-treatment observation period

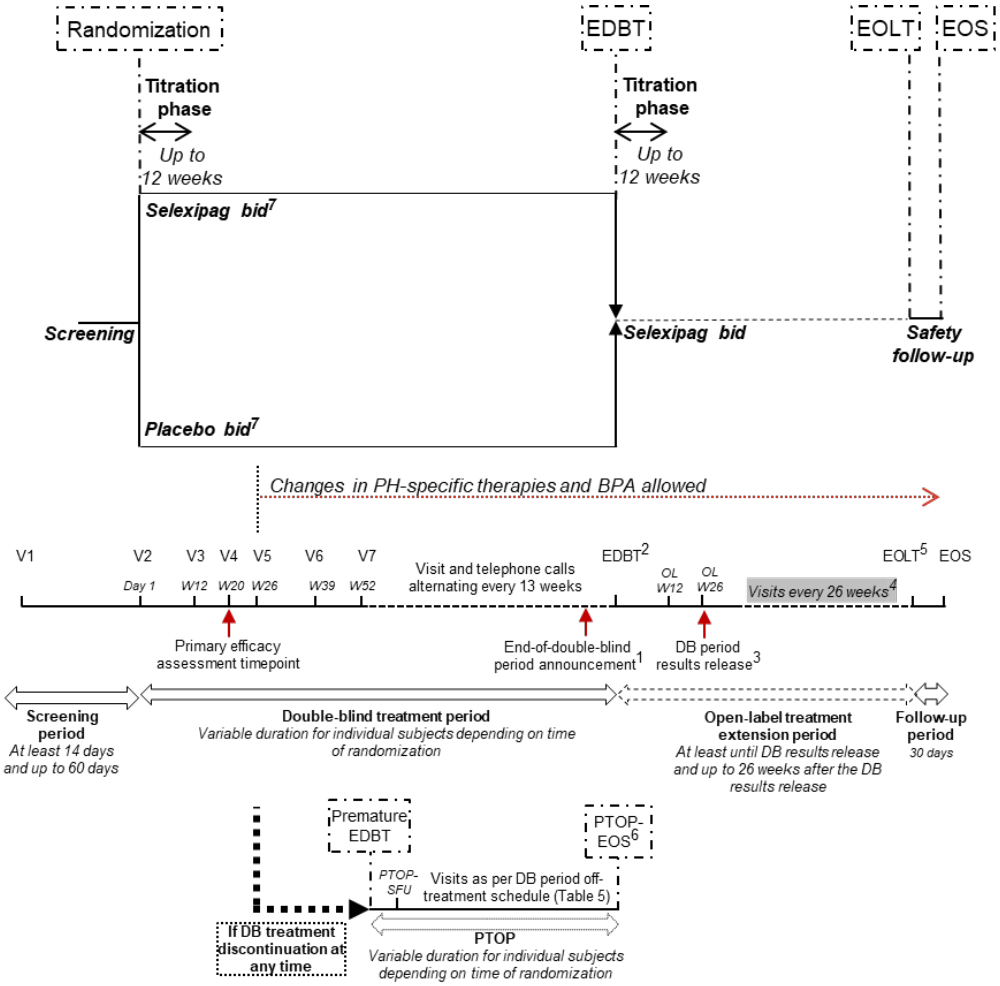
Subjects who prematurely discontinue the DB treatment period will enter a post-treatment observation period (PTOP) and will continue to perform the visits and assessments as

scheduled until the PTOP-EOS visit [see Section 5.1.10], provided the subject's consent for this limited participation in the study has not been withdrawn [see Section 8.2].

The visit schedule and protocol-mandated procedures for both hemodynamic and non-hemodynamic cohorts are performed according to the tables of assessments: Table 3 for DB treatment period, Table 4 for OL treatment period, and Table 5 for subjects entering the PTOP, as presented in Section 7.

The overall study design is depicted in Figure 1. The DB titration phase design is depicted in Figure 2.

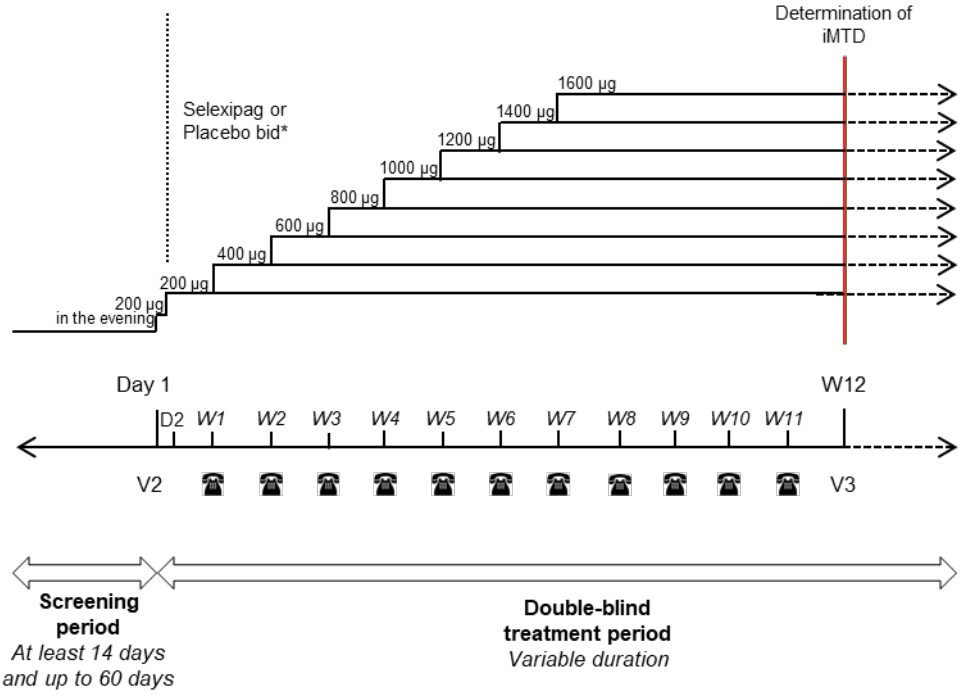
Figure 1 Study design



bid = twice daily; BPA = balloon pulmonary angioplasty; DB = double-blind, EDBT = End-of-Double-Blind-Treatment; EOLT = End-of-Open-Label-Treatment; EOS = End-of-Study; FU = follow-up, OL = open-label; PH = pulmonary hypertension; PTOP = post-treatment observation period, SFU = safety follow-up; V = visit; W = week.

(1) End-of-double-blind period announcement: when the overall target number of clinical worsening events has been reached, or earlier following recommendation of the IDMC or sponsor's decision.
(2) EDBT visit to occur within 4 weeks of End-of-double-blind period announcement [see (1)].
(3) DB period results to be released approx. 6 months after last EDBT/PTOP-EOS visit.
(4) *Variable duration of OL treatment extension period for individual subjects depending on time randomization, with visits every 26 weeks ONLY FOR SUBJECTS WHO WERE TRANSITIONED TO THE OL TREATMENT EXTENSION PERIOD BEFORE IMPLEMENTATION OF THE AC-065B302 PROTOCOL AMENDMENT 2.*
(5) EOLT visit to occur any time within 26 weeks of the DB period results release [see (3)].
(6) PTOP-EOS visit to occur within 4 weeks of End-of-double-blind period announcement [see (1)].
(7) For subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide), the dosing frequency of study treatment is once daily (qd), which must be taken in the morning [see Section 5.1.9].

Figure 2 Titration phase design



bid = twice daily; D = day; iMTD = individual maximum tolerated dose; V = visit; W = week. ☎ = weekly telephone calls.

* For subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide), the dosing frequency of the study treatment is once daily (qd), which must be taken in the morning [see Section 5.1.9].

If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to two weeks [see Section 5.1.3].

3.1.2 Study duration

The study starts with the first act of recruitment (ie, first Informed Consent Form [ICF] signed) and ends with the last telephone call or visit of the last subject.

The subjects will be treated in the DB treatment period for a variable duration depending on each subject's individual date of randomization. The maximum duration is estimated to be approximately 59 months (the actual duration depends on actual accrual rate and clinical worsening event rate [see Section 10.6.3] as well as recommendation of the IDMC [see Section 10.4] and sponsor's decision [Section 8.3]).

Subjects who complete the DB treatment period will enter the OL treatment extension period, which lasts at least until the release of results from the DB treatment period and up to a maximum of 26 weeks after the DB period results release.

Subjects who were transitioned to the OL treatment extension period before implementation of the AC-065B302 Protocol amendment 2: Those subjects transitioned to the OL treatment extension period after 52 weeks of DB treatment will be treated in the OL treatment period for a variable duration depending on each subject's individual date of randomization. They will remain in the OL treatment extension period until EOLT occurring anytime within 26 weeks of the DB period results release [see Figure 1 and Table 4].

Subjects who prematurely discontinue the DB study treatment will enter a PTOP and cannot enter the OL treatment extension period [see Section 3.1.1.4].

For an individual subject, the EOS visit is defined as the last telephone call / visit performed in the study [see Section 8.1].

The maximum duration of participation of a subject in the study will be approximately 74 months.

3.2 Study design rationale

3.2.1 Rationale for the use of placebo

A placebo-controlled study conducted in a randomized and DB fashion provides the most definite and rigorous method of evaluating treatment efficacy of a medical treatment and will allow establishment of the frequency and magnitude of changes in hemodynamic and clinical endpoints that may occur in the absence of active intervention. The use of placebo as a control will also allow proper evaluation of any safety-related events or abnormalities and disease progression observed during the study, and differentiation between events potentially related to the use of selexipag vs those related to the underlying disease.

A placebo-controlled study is considered ethically acceptable due to the eligibility criteria restricting enrollment to stable CTEPH subjects as an add-on to standard of care. The use of background therapy with PH-specific therapies (excluding prostanoids) is allowed. In addition, treatment escalation of PH-specific therapies and BPA are allowed following the Week 26 visit (Visit 5). Furthermore, subjects who complete the DB treatment will receive selexipag in the OL treatment extension period.

3.2.2 Rationale for the duration of the study

Subjects will receive DB selexipag or placebo for a variable duration (up to a maximum of 59 months) until EDBT visit. After the 90 subjects (approximately) of the hemodynamic

cohort have completed the Week 20 RHC (and LHC, if needed) (analysis time point 1), the primary endpoint (PVR) will be analyzed. If the study is not terminated prematurely for futility of PVR, the study will proceed as planned and the efficacy of selexipag on 6MWD (at Week 26), TTCW, and all-cause death or hospitalization related to PH-worsening, as well as other secondary endpoints will be assessed at specified time points [see Section 5.1.6.1] following the specified testing hierarchy [see Figure 4].

The results of the AC-055E201 (MERIT-1) study comparing macitentan to placebo showed a decrease in PVR of 16% when compared to placebo after 16 weeks of treatment and a significant increase in 6MWD after 24 weeks of treatment [Ghofrani 2017]. Exercise capacity increased gradually in this population, lagging behind hemodynamic improvements. Therefore, the durations of 20 and 26 weeks are considered to be sufficient to observe the effects on PVR and 6MWD, respectively, also allowing for titration to an iMTD. The variable follow-up time for individual subjects beyond Week 26 will allow for the assessment of the TTCW endpoint and the long-term safety and tolerability endpoints in a blinded fashion.

Access to selexipag beyond completion of the DB treatment is ensured by including the OL treatment extension period in the study. The OL treatment extension period will allow investigators to make an informed decision on post-study therapy based on the DB treatment period results and the actual intervention received by the study subjects. It will also help in collecting further long-term efficacy, safety and tolerability information on selexipag and the survival status of subjects with CTEPH who have already completed the DB treatment period.

3.2.3 Rationale for the post-treatment observation period

In order to estimate the effect of treatment initially assigned at baseline, regardless of adherence to the planned course of treatment (intent-to-treat principle), subjects who prematurely discontinue the DB treatment period will be followed up until the end-of-double-blind period, provided the subject's consent for this limited participation in the study has not been withdrawn.

3.3 Site personnel and roles

3.3.1 Heart catheterization

Detailed guidance on the conduct of RHC and LHC is provided in Appendix 1. Appropriate training(s) on the heart catheterization (HC) guidance must be completed and properly documented by site team members conducting the RHCs/LHCs.

3.3.2 6-minute walk test

Appropriate training(s) on the sponsor's 6-minute walk test (6MWT) guidelines [Appendix 3] must be completed and properly documented by site team members conducting the 6MWT.

3.4 Study committees

3.4.1 Steering committee

A Steering Committee (SC) has been appointed by the sponsor to contribute to the design of the protocol, oversee the conduct of the study, evaluate the results and support publications. The committee is governed by a dedicated SC charter.

3.4.2 Independent Data Monitoring Committee

An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is conducted with the highest scientific and ethical standards. The IDMC will interpret the results of the planned analyses at time points 1, 2, and 3 (which will be performed by the independent statistical support group [SSG]) as outlined in Section 10.4. The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter.

3.4.3 Adjudication committees

The study population includes subjects with CTEPH who are diagnosed as inoperable (ie, technically non-operable) or with persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment.

In accordance with the European Society of Cardiology and the European Respiratory Society Guidelines for the diagnosis and treatment of PH [Galiè 2016], an operability assessment for CTEPH subjects should be performed by a multidisciplinary CTEPH team.

Therefore, in addition to the CTEPH diagnosis, the inoperability and the persistence/recurrence of PH of CTEPH subjects considered eligible for study inclusion by the investigational sites will be confirmed by a multidisciplinary CTEPH team. For this purpose, two sets of independent adjudication committees (ACs) are established:

- Country-specific Adjudication Committees (CSACs) and
- Central Adjudication Committee (CAC) for countries without a CSAC.

The establishment of the ACs is contingent on sound experience, as per the requirements outlined in the ACs' charter. A CSAC may be established to review subjects' data from selected countries within a specific geographical region.

These committees will review predefined data for each subject and assess whether the CTEPH diagnosis and persistence/recurrence of PH (when applicable) are confirmed and the inoperability criterion is met prior to randomization [see Section 4.1.1].

In addition to the eligibility review, the ACs will review the post-baseline RHC/LHC of each subject in the hemodynamic cohort in order to confirm the scientific and medical plausibility of all Week 20 hemodynamic parameters as compared to the baseline values. The ACs will provide the sponsor with feedback on the quality and plausibility. The plausibility check may lead to site querying from the sponsor of the values reported on the electronic Case Report Forms (eCRFs); no independent RHC/LHC values will be provided by the AC. Protocol deviations will be assigned for all Week 20 RHCs/LHCs not meeting the above quality criteria or any non-plausible Week 20 hemodynamic parameters.

The composition and operation of these committees is described in the ACs' charter.

3.4.4 Clinical Event Committee

A Clinical Event Committee (CEC) has been appointed by the sponsor to adjudicate, in a blinded fashion, components of the clinical worsening events. Full details for this procedure, as well as the composition and operation of the CEC, are described in the CEC charter.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adult male and female subjects aged ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤85 years with an established diagnosis of inoperable CTEPH (ie, technically non-operable) or persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment, as confirmed by the corresponding ACs (CSAC or CAC) [see Section 3.4.3]. The subject must have PH in WHO FC I–IV due to CTEPH (Group 4.1 of PH).

To minimize the number of screening failures, it is recommended to only screen subjects with available imaging and hemodynamic data, as described in Section 7.2.2 and Section 7.2.3.1.

Eligible subjects must be able and willing to give informed consent for participation in the clinical study.

4.1.1 Adjudication procedure

Following the Screening visit, for subjects judged to have inoperable (ie, technically non-operable) or recurrent/persistent CTEPH after surgical (PEA) and/or interventional (BPA) treatment by the investigational site and fulfilling all other eligibility criteria, the

ACs (CSAC or the CAC) will receive anonymized data as outlined in Table 1 and detailed in the AC charter.

Table 1 Data required for adjudication procedure

	Inoperable CTEPH	Persistent/recurrent CTEPH after BPA	Persistent/recurrent CTEPH after PEA[b]
RHC (and LHC, if needed)[a]	X	X	X
Imaging assessments	≥2[c]	≥1[d]	≥1[d]
Historical surgery & intervention report	–	X	X
Medical history form	X	X	X

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

a. RHC (and LHC, if needed) must be performed at least 90 days after start of full anticoagulation and at least 90 days after last surgical (PEA) or interventional (BPA) treatment for subjects with persistent/recurrent CTEPH.
For the hemodynamic cohort, a historical RHC (and LHC, if needed) is allowed, provided it was performed within 30 days prior to Screening*, at least 90 days after last change in PH-specific therapies (ie, change in dose or initiation of new class of drugs) and as per guidance in Appendix 1.
For the non-hemodynamic cohort, a historical RHC (and LHC, if needed) is allowed, provided it was performed within 6 months prior to Screening*.
If no historical results are available, an RHC (and LHC, if needed) must be performed during the Screening period (as per guidance in Appendix 1 for the hemodynamic cohort).
* In case of rescreening in the hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit. In case of rescreening in the non-hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used.

b. Includes PEA followed by BPA.

c. Ventilation/perfusion (V/Q) scan, pulmonary angiography (PA), computed tomography pulmonary angiogram (CTPA), magnetic resonance angiography (MRA) performed in the 14-month period prior to randomization.

d. V/Q scan, PA, CTPA, MRA performed in the 14-month period prior to randomization and after last surgical (PEA) and/or interventional (BPA) treatment.

These data will be transferred from the investigational site to the corresponding AC via a central image processing center. Based on these data, the AC will assess the eligibility of each subject.

The investigator will await the feedback from the AC concerning the final eligibility before informing the subject and performing the randomization visit.

In addition to the eligibility review, the scientific and medical plausibility check will also be performed by the ACs via a central image processing center.

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

4.2 Rationale for the selection of the study population

The study population includes subjects with inoperable (ie, technically non-operable) or persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment. This population is generally considered a good candidate for medicinal treatment to treat PH and accompanying right heart failure [Galiè 2016]. At present, the only approved treatment for CTEPH is riociguat, which is contraindicated in combination with a PDE-5 inhibitor [Adempas® SmPC, Adempas® USPI]. The targeted study population was chosen as it represents a broad spectrum of CTEPH patients with and without PH-specific background therapies. Additionally, there is a medical need for an approved therapy in this indication acting on the prostacyclin pathway, allowing for combination therapy with other PH-specific therapies.

4.3 Inclusion criteria

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

1. Signed and dated ICF.
2. Male and female subjects ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤85 years old at Screening (Visit 1).
3. Subjects with diagnosis of CTEPH and inoperability confirmed by the corresponding AC (CSAC or CAC) [see Section 3.4.3], defined as one of the following options:
    a. Inoperable CTEPH (ie, technically non-operable) with:
    – Diagnosis of CTEPH based on at least two of the following assessments performed in the 14-month period prior to randomization (Visit 2):
        - ventilation/perfusion (V/Q) scan,
        - pulmonary angiography (PA),
        - computed tomography pulmonary angiogram (CTPA), and/or
        - magnetic resonance angiography (MRA).

- RHC (and LHC if needed)[1] performed at least 90 days after start of full anticoagulation, showing:
  - PVR at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units for the hemodynamic cohort and PVR at rest ≥300 dyn.sec/cm^5 or ≥3.75 Wood units for the non-hemodynamic cohort,
  - mPAP ≥25 mmHg,
  - Pulmonary arterial wedge pressure (PAWP) ≤15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) ≤15 mmHg.

b. Persistent/recurrent CTEPH after BPA, and deemed inoperable with:
   - Diagnosis of CTEPH based on at least one of the following assessments performed in the 14-month period prior to randomization (Visit 2) and after last interventional (BPA) treatment: V/Q scan, PA, CTPA or MRA.
   - RHC (and LHC, if needed)[1] performed at least 90 days after last interventional (BPA) treatment and at least 90 days after start of full anticoagulation. showing:
     - PVR at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units for the hemodynamic cohort and PVR at rest ≥300 dyn.sec/cm^5 or ≥3.75 Wood units for the non-hemodynamic cohort,
     - mPAP ≥25 mmHg,
     - PAWP ≤15 mmHg, or, if not available or unreliable, an LVEDP ≤15 mmHg.

c. Persistent/recurrent CTEPH after PEA (including PEA followed by BPA) with:
   - Diagnosis of CTEPH based on at least one of the following assessments performed in the 14-month period prior to randomization (Visit 2) and after last surgical (PEA) or interventional (BPA) treatment: V/Q scan, PA, CTPA or MRA.

[1] For the hemodynamic cohort, a historical RHC/LHC is allowed, provided it was performed within 30 days prior to Screening*, at least 90 days after last change in PH-specific therapies (i.e., change in dose or initiation of new class of drugs) and as per guidance in Appendix 1.
For the non-hemodynamic cohort, a historical RHC/LHC is allowed, provided it was performed within 6 months prior to Screening*.
* In case of rescreening in the hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit. In case of rescreening in the non-hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used.
If no historical results are available, an RHC/LHC must be performed during the Screening period (as per guidance in Appendix 1 for the hemodynamic cohort).

- RHC (and LHC, if needed)[1] performed at least 90 days after last surgical (PEA) or interventional (BPA) treatment and at least 90 days after start of full anticoagulation, showing:
  - PVR at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units for the hemodynamic cohort and PVR at rest ≥300 dyn.sec/cm^5 or ≥3.75 Wood units for the non-hemodynamic cohort,
  - mPAP ≥25 mmHg,
  - PAWP ≤15 mmHg, or, if not available or unreliable, an LVEDP ≤15 mmHg.

4. PH in WHO FC I–IV.
5. Subject able to perform the 6MWT with a minimum distance of 100 m and a maximum distance of 450 m at Screening visit (Visit 1).
6. A woman of childbearing potential [see definition in Section 4.5.1] is eligible only if all the following applies:
   a. Negative serum pregnancy test at Screening and a negative urine pregnancy test at randomization.
   b. Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation.
   c. Agreement to use one of the methods of birth control described in Section 4.5 from Screening visit up to at least 30 days after study treatment discontinuation. If a hormonal contraceptive is chosen, it must be taken for at least 1 month prior to randomization.

4.4 Exclusion criteria

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

4.4.1 Exclusion criteria related to the disease

1. Planned BPA within 26 weeks after randomization.
2. Change in dose or initiation of new PH-specific therapy within 90 days prior to the baseline RHC (and LHC, if needed) qualifying for enrollment for the hemodynamic cohort and within 90 days prior to randomization (Visit 2) for the non-hemodynamic cohort.
3. Treatment with prostacyclin (epoprostenol), prostacyclin analogs (ie, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/Uptravi®) within 90 days prior to randomization (Visit 2), except those given at vasodilator testing during RHC.
4. Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to baseline RHC (and LHC, if needed).

4.4.2 Exclusion criteria related to comorbidities

5. Severe coronary heart disease or unstable angina as assessed by the investigator.
6. Myocardial infarction within the last 6 months prior to or during Screening.
7. Decompensated cardiac failure if not under close supervision.
8. Severe arrhythmias as assessed by the investigator.
9. Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months prior to or during Screening.
10. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH.
11. Known or suspicion of pulmonary veno-occlusive disease (PVOD).

4.4.3 Exclusion criteria related to selexipag use

12. Known and documented severe hepatic impairment eg, Child-Pugh Class C.[2]
13. Severe renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2 or serum creatinine >2.5 mg/dL or 221 µmol/L) at Screening.
14. Known or suspected uncontrolled thyroid disease as per investigator judgment.
15. Pregnant, planning to be become pregnant or lactating.
16. Treatment with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; eg, gemfibrozil) or moderate inducers of CYP2C8 (eg, rifampicin) within 14 days prior to randomization.
17. SBP <90 mmHg at Screening (Visit 1) or at Randomization (Visit 2).
18. Known hypersensitivity to selexipag or drugs of the same class, or any of their excipients.

4.4.4 General exclusion criteria

19. Planned or current treatment with another investigational treatment up to 3 months prior to randomization.
20. Any co-morbid condition that may influence the ability to perform a reliable and reproducible 6MWT, including use of walking aids (cane, walker, etc.).
21. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease.
22. Known concomitant life-threatening disease with a life expectancy <12 months.

[2] The assessment of hepatic impairment (Child-Pugh Score as per Appendix 10) must be fully documented for patients who have clinical signs and evidence (from central and/or local lab) of hepatic impairment.

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

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

4.5.2 Acceptable methods of contraception

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 hospital chart.

Women of childbearing potential [see definition in Section 4.5.1] must use one of the following methods of birth control from Screening visit up to at least 30 days after study treatment discontinuation:

1. Diaphragm; female condom or cervical cap; or partner's use of a condom, and any of these used in combination with a spermicide.
2. Intra-uterine devices.
3. Oral or injectable contraceptive agents, implants or transdermal contraceptive hormone patches. If a hormonal contraceptive is chosen, it must be taken for at least 1 month prior to randomization. For hormonal contraceptive initiated during the study, this must overlap for at least 1 month with the existing contraceptive method.
4. Sterilization method (tubal ligation / occlusion or partner's vasectomy).
5. True abstinence from intercourse with a male partner, only when this is in line with the preferred lifestyle of the subject.

Rhythm methods are not considered as acceptable methods of contraception for this study.

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

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment and matching placebo: Description and rationale

DB selexipag 200 µg, matching placebo and OL selexipag 200 µg will be provided as identical yellow, round, non-debossed, film-coated tablets in childproof bottles containing 120 tablets.

The DB study treatment refers to either DB selexipag 200 µg or the matching placebo, administered during the DB treatment period. The OL study treatment refers to OL selexipag 200 µg, administered during the OL treatment period. If not otherwise specified, study treatment refers to both DB and OL study treatments.

5.1.2 Study treatment administration

The study treatment is administered orally.

The tablets should be swallowed whole with water. They should not be crushed, split or chewed.

Dosing frequency will be twice daily (bid), with an interval of approximately 12 hours. For subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide), the dosing frequency is once daily (qd) [see Section 5.1.9].

At the beginning of each up-titration step, the first dose is to be taken in the evening in order to reduce the likelihood of the occurrence of IP-receptor-agonist-associated AEs [see Section 5.1.11.1]. In case of qd dosing, the subjects must take the study treatment in the morning.

Tolerability may improve when study treatment is taken with food. To avoid fluctuations in drug exposure, it is recommended that study treatment is consistently taken either with or without food. In addition, side effects have been observed to respond to symptomatic treatment [see Section 5.1.11.1].

Depending on the iMTD, a single dose of study treatment will consist of 1–8 tablets (200-1600 µg).

5.1.3 Study treatment up-titration

The DB [Section 5.1.3.1] and OL [Section 5.1.3.2] study treatments must be up-titrated to allow each subject to reach their iMTD, in the range of 200–1600 µg bid/qd.

Any study treatment interruption of three consecutive days (or six consecutive doses if bid regimen or three consecutive doses if qd regimen) or more will require a new up-titration to avoid tolerability-limiting side effects [see Section 5.1.9].

Any dose change must be documented in the eCRF.

5.1.3.1 Double-blind study treatment up-titration

The first intake of DB treatment could take place on-site or at home. Each subject will start with one tablet of DB study treatment, ie, selexipag (200 µg) or matching placebo, in the evening of Day 1 (randomization visit, Visit 2) and will continue with 200 µg bid on Day 2. Subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking moderate CYP2C8 inhibitor(s) will start with 200 µg qd in the morning of Day 2.

If the dose is well tolerated, the dose will be up-titrated in 200 µg bid/qd increments at weekly intervals during scheduled telephone calls or visits until reaching the iMTD [see Figure 2 and Table 2].

If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to two or more weeks.

The decision not to further up-titrate the dose will be at the discretion of the investigator's medical judgment based on the occurrence and severity of typical pharmacological effects of IP-receptor agonists [see Section 5.1.11.1] and the subject's individual tolerability.

If needed, the dose can be reduced by 200 µg bid/qd.

Although up-titration intervals can be flexible, the total time to reach the iMTD is 12 weeks. At Week 12 (Visit 3), the dose reached for each subject is defined as the iMTD. This dose must be kept stable at least until Week 26 (Visit 5) but can be adjusted for safety and tolerability reasons.

After Week 26, investigators will be allowed to up-titrate the dose of the subject further if needed (up to the maximum of 1600 µg bid/qd, as applicable) in 200 µg bid/qd increments and only at site visits (scheduled or unscheduled visits). Dose reduction for safety and tolerability reasons will also be allowed after Week 26.

Table 2 Double-blind dosing scheme

Period	Dose regimen	Duration	
First dose	200 µg	On Day 1 in the evening (p.m.)	1 tablet
Up-titration	200 µg bid*, §	From Day 2 a.m. to Day 8 a.m.**	1 tablet bid§
	400 µg bid*, §	From Day 8 p.m. to Day 15 a.m.**	2 tablets bid§
	600 µg bid*, §	From Day 15 p.m. to Day 22 a.m.**	3 tablets bid§
	800 µg bid*, §	From Day 22 p.m. to Week 4 a.m.**	4 tablets bid§
	1000 µg bid*, §	From Week 4 p.m. to Week 5 a.m.**	5 tablets bid§
	1200 µg bid*, §	From Week 5 p.m. to Week 6 a.m.**	6 tablets bid§
	1400 µg bid*, §	From Week 6 p.m. to Week 7 a.m.**	7 tablets bid§
	1600 µg bid*, §	From Week 7 p.m. to Week 12 a.m.**	8 tablets bid§
Maintenance	iMTD: 200-1600 µg bid§	From Week 12 throughout the double-blind treatment period (or until Week 26)	1–8 tablets bid §

a m. = morning; bid = twice daily; iMTD = individual maximum tolerated dose; p m. = evening.
* Or the iMTD until Week 12.
** If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to two or more weeks. If needed, the dose can be reduced by 200 µg bid/qd.
§ For subjects with moderate hepatic impairment (Child-Pugh B) and who are concomitantly taking moderate CYP2C8 inhibitors, the dosing frequency is once daily, which must be taken in the morning [see Section 5.1.9].

Beginning with the morning of Visit 3, and at each visit thereafter, subjects must take the morning dose before any visit-related procedure.

5.1.3.2 Open-label study treatment up-titration

The subjects, investigator and study personnel; site managers (SM); sponsor personnel; and Contract Research Organization (CRO) personnel will remain blinded to subjects' treatment assignment at the time of transition to the OL period. Therefore, all subjects entering the OL study treatment period will have to up-titrate OL selexipag, irrespective of the previous treatment assignment. The last DB study treatment dose must be taken in the morning before performing EDBT visit.

The first intake of OL treatment could take place on-site or at home. The OL study treatment up-titration will start with one tablet of OL selexipag (200 µg) in the evening of EDBT visit and with 200 µg bid on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking moderate CYP2C8

inhibitor(s) will start with one tablet of OL selexipag (200 µg) in the morning of the day after EDBT visit.

The up-titration procedure will then be similar to the one described in Section 5.1.3.1. Depending on the tolerability, the dose will be up-titrated by the investigator/delegate in 200 µg bid/qd increments at weekly intervals during scheduled telephone calls until reaching the iMTD. The duration of the titration step can be prolonged to two or more weeks. Although up-titration intervals can be flexible, the total time to reach the iMTD is 12 weeks. If needed, the dose can be reduced by 200 µg bid/qd.

After OL-Week 12, investigators will be allowed to up-titrate the dose of the subject further if needed (up to the maximum of 1600 µg bid/qd, as applicable) in 200 µg bid/qd increments and only at site visits (scheduled or unscheduled visits). Dose reduction for safety and tolerability reasons will also be allowed after OL-Week 12.

Beginning with the morning of OL-Week 12 Visit, and at each visit thereafter, subjects must take the morning dose before any visit-related procedure.

5.1.4 Treatment assignment

After the ICF has been signed, the investigator/delegate contacts the Interactive Response Technology (IRT) system at Visit 1 (Screening visit) to obtain a subject number.

In case of rescreening, the subject number attributed at the time of first screening will be used for the rescreened subject.

At Visit 2 (randomization visit), after having verified that the subject meets all inclusion criteria (including confirmation of CTEPH and inoperability by the corresponding AC [CSAC or CAC]) and none of the exclusion criteria, the investigator/delegate contacts the IRT system to randomize the subject. The IRT assigns a unique randomization number to the subject 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 CRO, Almac Clinical Technologies, using SAS® version 9.4.

At randomization (Visit 2), treatment allocation will be stratified by treatment with PH-specific therapies (ie, ERAs, PDE-5 inhibitor, sGC stimulator [riociguat]; one versus two versus naive [capped at 40%]) and by CTEPH population (inoperable [with or without BPA] versus persistent-recurrent after PEA [including PEA followed by BPA]). Subjects will be randomized in a 1:1 ratio to either selexipag or placebo. Further details are provided in the IRT specification document.

5.1.5 Blinding

The first treatment period of this study up to EDBT will be performed in a DB fashion. The investigator and study personnel, the subjects, the SMs, sponsor personnel and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until the fourth analysis time point [see Section 5.1.6], ie, when all randomized subjects have completed EDBT/PTOP-EOS Visit or prematurely discontinued from the study, and when the DB database is locked and the data extract is performed, or when the study is terminated prematurely. Sponsor personnel responsible for clinical study supply distribution will need to be unblinded at a supply level to ensure adequate supply of study treatment. These persons will be clearly identified with their unblinding documented in the Trial Master File. A dedicated submission team, independent from the Clinical Trial Team (CTT), will be unblinded at analysis time points 2 and 3, as appropriate [see Section 5.1.6.3].

Until the time of sponsor unblinding [see Section 5.1.6], the randomization list is kept strictly confidential and accessible only to authorized persons (ie, an independent SSG and Secure Data Office [SDO]), who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

5.1.6 Unblinding

5.1.6.1 Timing of study analyses

The database will be locked, and the data will be extracted and analyzed at five planned analysis time points during the study [see Figure 3]:

1) The first analysis time point will be when approximately 90 randomized subjects, the hemodynamic cohort, have completed the Week 20 RHC (and LHC, if needed) or prematurely discontinued from the study. The final analysis of the PVR endpoint will be performed by the independent SSG for the IDMC. Actions to be taken following this analysis are described in Section 10.4.

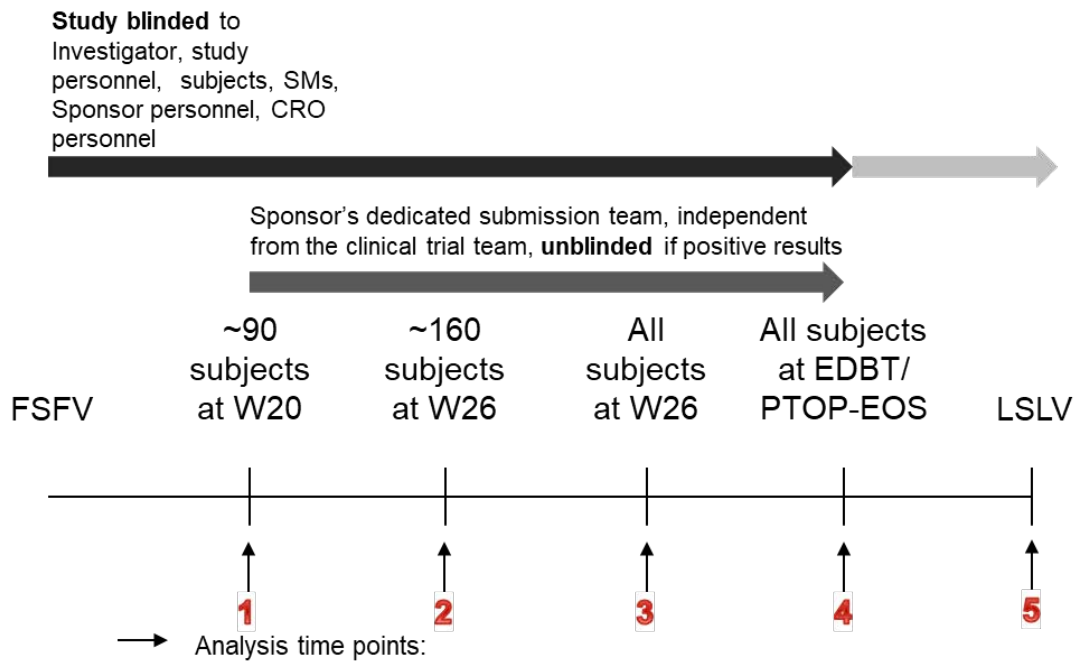
2) The second analysis time point will be when approximately 160 randomized subjects have completed the Week 26 6MWD assessment or prematurely discontinued from the study. An interim analysis (IA) for the 6MWD endpoint and an IA for the TTCW endpoint will be performed by the independent SSG for the IDMC. Actions to be taken following these analyses are described in Section 10.4. If regulatory submissions are to be prepared, all available data will be analyzed according to the statistical analysis plan (SAP) for regulatory submissions by the sponsor's dedicated submission team, independent from the CTT.

3) The third analysis time point will be when all (up to 280) randomized subjects have completed the Week 26 6MWD assessment or prematurely discontinued from the study. The final analysis of the 6MWD endpoint and an IA for the TTCW endpoint will be performed by the independent SSG for the IDMC. Actions to be taken following these analyses are described in Section 10.4. If regulatory submissions are to be prepared, all available data will be analyzed according to the SAP for regulatory submissions by the sponsor's dedicated submission team, independent from the CTT.

4) The fourth analysis time point will be when all (up to 280) randomized subjects have completed the DB treatment period, or the PTOP or prematurely discontinued from the study. The DB database will be locked, the data extract will be performed and unblinding will occur at this time point. This final analysis of the DB treatment period will be conducted by the sponsor. If regulatory submissions are to be prepared, all data will be analyzed according to the SAP for regulatory submissions by the sponsor.

5) The fifth analysis time point will be when all (up to 280) randomized subjects have performed their EOS visit. An analysis including the OL period data will be performed by the sponsor. This analysis will be considered the final analysis of the study.

Figure 3 Study analyses



1 When approximately 90 subjects have performed the W20 RHC (and LHC, if needed) assessment:
- Final analysis of PVR endpoint

2 When approximately 160 subjects have performed the W26 6MWD assessment or prematurely discontinued from the study:
- Interim analysis of 6MWD endpoint
- Interim analysis of TTCW endpoint

3 When all subjects (up to 280) have performed the W26 6MWD assessment or prematurely discontinued from the study:
- Final analysis of 6MWD endpoint
- Interim analysis of TTCW endpoint

4 When all subjects (up to 280) have performed EDBT/PTOP-EOS visit or prematurely discontinued from the study:
- Final analysis of DB period

5 When all subjects (up to 280) have performed EOS visit:
- Final analysis of the study

6MWD = 6-minute walk distance; CRO = Contract Research Organization; EDBT = End-of-Double-Blind-Treatment; FSFV = First subject first visit; LHC = Left heart catheterization; LSLV = Last subject last visit; PTOP-EOS = Post-treatment observation period end-of-study; PVR = pulmonary vascular resistance; RHC = Right heart catheterization; SM = Site manager; TTCW = Time to clinical worsening; W = week.

The diagram is not to scale.

5.1.6.2 Unblinding for IDMC

An independent SSG not otherwise involved in the design, conduct and 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 randomization code will be made available to the independent SSG in accordance with the sponsor's Quality System (QS) documents.

5.1.6.3 Unblinding for analysis time points 1, 2, and 3

For the first three analysis time points, full randomization information of all subjects randomized so far will be made available to the independent SSG for analysis [see Section 5.1.6.2]. In accordance with the IDMC charter, the IDMC will review the results and provide a recommendation on continuation or premature study termination. If regulatory submissions are to be prepared, randomization information will be made available to a sponsor's independent team dedicated for submission. The safeguards taken to keep the dedicated submission team independent from the CTT will be described in a separate charter.

5.1.6.4 Unblinding for the fourth analysis time point (end-of-double-blind-treatment period)

Full randomization information will be made available for data analysis only after all randomized subjects have completed the DB treatment period or the PTOP or prematurely discontinued from the study, and when the DB part of the database is locked and the data extract is performed, in accordance with current standard operating procedures [see Figure 3]. Following each subject's completion of the DB treatment period, they will enter the OL extension period. In order to preserve the blind of each individual subject until the DB database will be locked, all subjects will be up-titrated with OL selexipag [see Section 5.1.3.2].

5.1.6.5 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, the sponsor Global Drug Safety 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.

5.1.6.6 Emergency procedure for unblinding

The investigator, study personnel and sponsor personnel must remain blinded to the subject's treatment assignment up to the fourth analysis time point. The identity of the study treatment may be revealed only if the subject 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. 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 subject, 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.

A subject may stay on study treatment after unblinding provided the following conditions are met: emergency unblinding for accidental or intentional overdose or medication error.

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

5.1.7 Study treatment supply

Manufacturing, labeling, packaging and supply of study treatment will be conducted according to Good Manufacturing Practice, 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 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

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

5.1.7.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used, and unused study treatment bottles at each visit. The protocol-mandated study-treatment dispensing procedures may not be altered without prior written approval from the sponsor. The IRT will allow dispensation of study treatment outside the scheduled visit. An accurate record

of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.7.4 Study treatment return and destruction

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

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 subject (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, bottle dispensed to the subject):

- Dispensed bottles number
- Date dispensed / number of tablets dispensed
- Date returned / number of tablets returned

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

If the subject forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any tablets from the remaining study treatment bottle and to return it at the next visit.

5.1.8.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated by site personnel at each visit using the below formula and entered in the eCRF:

Compliance = [(number of tablets dispensed − number of tablets returned) / total number of tablets that should have been taken during the period[3]] × 100.

Between-visit and overall study compliance are expected to be between 80% and 120%. Compliance values outside of this range will be considered as a protocol deviation, which will be reported by the SM. The investigator must discuss any non-compliance with the subject 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

For subjects who are unable to tolerate the protocol-specified dosing scheme, dose adjustments must follow the down-titration instructions [see Sections 5.1.3.1 and 5.1.3.2].

Dosing frequency of the study treatment must be qd (study treatment to be taken in the morning), when the subject presents with moderate hepatic impairment (Child-Pugh B) or when a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide) is co-administered. Dosing frequency must be changed to bid when moderate hepatic impairment resolves or when co-administration of the moderate CYP2C8 inhibitor is stopped.

The effect of strong inhibitors of UGT1A3 and UGT2B7 (eg, valproic acid, probenecid, and fluconazole) on the exposure to selexipag and its active metabolite has not been studied. Caution is required when administering these medicinal products concomitantly with selexipag. A potential pharmacokinetic interaction with strong inhibitors of UGT1A3 and UGT2B7 cannot be excluded [Selexipag IB].

In case of concomitant administration of a moderate inducer of CYP2C8 (eg, rifampicin), dose adjustment of selexipag/placebo may be required because of drug-drug interactions. A drug-drug interaction study showed that rifampicin did not lead to a relevant change in exposure to selexipag, whereas exposure to the active metabolite decreased by half [Selexipag IB].

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.

[3] The period is defined as the number of days of treatment from the date of start of study treatment until the next accountability visit. The number of tablets that should have been taken is derived from the number of days in the corresponding period. Tablets that are not taken following study staff instructions to interrupt study treatment are not counted as tablets that should have been taken.

If study treatment is interrupted by the subject for any reason, she/he must immediately inform the investigator.

Any study treatment interruption of three consecutive days (or six consecutive doses if bid regimen or three consecutive doses if qd regimen) or more will require a new up-titration to avoid tolerability-limiting side effects. Subjects will start again with one tablet of study treatment (200 µg) bid/qd as applicable. If this dose is well tolerated, the dose will be up-titrated by the investigator/delegate in 200 µg increments up to the iMTD before study treatment interruption [see Section 5.1.3]. For each subject, the up-titration frequency will be up to the medical judgment of the investigator and based on his/her clinical evaluation of the subject's tolerability of the study treatment prior to its interruption.

Interruptions of study treatment must be kept as short as possible. If treatment is stopped for more than 14 consecutive days (or 28 consecutive doses if bid regimen or 14 consecutive doses if qd regimen), 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 subject, the investigator or sponsor personnel. The main reason for discontinuation of study treatment and whether the decision was that of the subject (eg, due to an AE or lack of efficacy), the investigator (eg, due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy) or the sponsor (eg, study termination) must be documented in the eCRF.

A subject 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 subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, the investigator will make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

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

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

A subject who prematurely discontinues study treatment is <u>NOT considered</u> withdrawn from the study:

- A subject **who prematurely discontinues DB study treatment** will enter a PTOP [see Section 3.1.1.4], provided the subject's consent for this limited participation in the study has not been withdrawn [see definition in Section 8.2]. The subject will be asked to return for a premature EDBT visit within 7 days of last intake of DB study treatment and will be contacted for a safety follow-up call 30 (+5) days after the last intake of DB study treatment (PTOP- safety follow-up [SFU]) . At the premature EDBT visit, the assessments described for the regular EDBT visit are to be performed [see Table 3].

  Thereafter, the subject will continue to perform the visits and assessments as scheduled [see Table 5] until the PTOP-EOS, which occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC [see Section 10.4], or sponsor's decision [see Section 8.3].

  If the premature EDBT visit or the PTOP- SFU call falls within the time window of any other scheduled visit, these visits can be combined, and assessments will not be repeated.

- If a subject **discontinues prematurely DB study treatment and does not agree to enter the PTOP** (ie, continue to perform the visits and assessments as scheduled until the PTOP-EOS visit), he/she will be asked to return for the premature EDBT visit within 7 days of last intake of DB study treatment and will be contacted for a SFU phone call 30 (+5) days after the last intake of DB, provided the subject's consent for this limited participation in the study has not been withdrawn.

  Long-term survival follow-up information [see Section 7.2.3.9] will then be collected yearly until death or end-of-double-blind period announcement (ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor decision), provided the subject's consent for this limited participation in the study has not been withdrawn.

- A subject who **prematurely discontinues OL study treatment** will be followed up until 30 (+5) days after OL study treatment discontinuation, provided that the subject's consent for this limited participation in the study has not been withdrawn. The subject will be asked to return for a premature EOLT visit within 7 days of last intake of OL study treatment and will be contacted for a safety follow-up call 30 (+5) days after the last intake of OL study treatment. At the premature EOLT visit, the assessments described for the regular EOLT visit are to be performed [see Table 4].

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered to be withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 8.2 and 8.4, respectively.

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

Study treatment interruptions exceeding 14 consecutive days (or 28 consecutive doses if bid regimen or 14 consecutive doses if qd regimen) must lead to permanent discontinuation of study treatment. In that case, the premature EDBT/EOLT visit must occur within 7 days of the discontinuation criteria being met.

Any study treatment interruption of three days (or six consecutive doses if bid regimen or three consecutive doses if qd regimen) or more will require new up-titration [see Section 5.1.9].

Interruptions of one dose or more must be recorded on the study treatment log in the eCRF.

5.1.11.1 Tolerability issues / AEs

Adverse reactions associated with the mode of action of selexipag have been observed frequently, in particular during the phase of individualized dose titration. These included: headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia and flushing. In adult subjects with PAH, these effects were usually transient or manageable with symptomatic treatment. Gastrointestinal events have been observed to respond to antidiarrheal, antiemetic and anti-nausea medicinal products and/or medicinal products for functional gastrointestinal disorders. Pain-associated events have frequently been treated with analgesics (such as paracetamol/acetaminophen).

However, if a subject reaches a dose that cannot be tolerated and is not manageable, the investigator should follow the instructions given in Sections 5.1.3.1 and 5.1.3.2.

5.1.11.2 Hepatic impairment

If hepatic impairment is suspected, a clinical assessment of severity (eg, Child-Pugh score) must be performed and fully documented. If a subject has developed severe hepatic impairment (Child-Pugh C, see Appendix 10) at any time during the study, the study treatment must be permanently discontinued.

5.1.11.3 Pulmonary edema due to PVOD

Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered. If confirmed, the study treatment must be discontinued.

5.1.11.4 Initiation of prohibited medications

Study treatment must be permanently discontinued if strong inhibitors of CYP2C8 (eg, gemfibrozil) and/or any investigational treatments are started during the DB and/or OL treatment period.

5.1.11.5 Pregnancy

If a female subject becomes pregnant while on study treatment, study treatment must be discontinued, and the investigator should arrange for specific therapy as needed [Regitz-Zagrosek 2011]. For reporting of pregnancies, refer to Section 9.3.1.

5.1.12 Treatment of overdose

For this study, any single dose greater than 1600 µg or a total daily dose greater than 3200 µg will be considered an overdose. For subjects with moderate hepatic impairment or who are concomitantly taking moderate (a) CYP2C8 inhibitor(s) the dosing frequency is once daily, and an overdose is defined by the intake of a dose greater than 1600 µg or a total daily dose greater than 1600 µg.

Isolated cases of overdose up to 3200 µg micrograms have been reported. Mild, transient nausea was the only reported consequence.

In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein bound.

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

- Contact the sponsor immediately.
- Evaluate the subject to determine, in consultation with the sponsor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the subject for AE/SAE and laboratory abnormalities until selexipag can no longer be detected systematically (at least 3 days)
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

5.2 Previous and concomitant medications

5.2.1 Definitions

A previous medication / non-pharmacological therapy is any treatment for which the end date is prior to signing of informed consent.

A medication / non-pharmacological therapy that is study-concomitant is any treatment that is ongoing or initiated after signing of informed consent or initiated up to the EOS as defined in Section 8.1.

A medication / non-pharmacological therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the DB and/or OL treatment period.

An auxiliary medicinal product is a medicinal product used for the purpose of the clinical study but not as an investigational medicinal product (eg, a mandatory background therapy or a medicinal product used for a study-mandated procedure).

5.2.2 Recording of previous/concomitant medications / auxiliary medicinal products / procedures 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. All previous medications must be recorded in the eCRF if discontinued less than 30 days prior to signing of the informed consent. Any previous PH-specific therapies (ERA, PDE-5 inhibitors, riociguat) must be recorded in the eCRF if discontinued less than 90 days prior to the baseline RHC (and LHC, if needed). 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.

Information on the indication, start/end dates of procedures will be collected in the eCRF.

5.2.3 Auxiliary medicinal products

All subjects must receive full anticoagulation treatment, as per local practice, from 90 days prior to the baseline RHC (and LHC, if needed) assessment and up to EOS. During the study, the usual safety measures, as routinely used by the study site for cessation of anticoagulants drugs, prior to and after the RHC/LHC procedure, should be taken.

Interruption of anticoagulant drugs due to an AE during the course of the study is allowed.

5.2.4 Allowed concomitant therapy

- BPA procedure after Week 26 (Visit 5).
- Change in dose or initiation of new PH-specific therapies (ie, ERA, PDE-5 inhibitor, sGC stimulator) after Week 26 (Visit 5).
- Single administration of prostacyclin or analogs during the RHC procedure for acute vasodilator testing.
- Treatment with moderate inhibitors of CYP2C8 (eg, clopidogrel, deferasirox, teriflunomide) with study-treatment dose adjustment as described in Section 5.1.9.

5.2.5 Forbidden concomitant therapy

- Change in dose or initiation of new PH-specific therapies (ie, ERA, PDE-5 inhibitor, sGC stimulator) from 90 days prior to randomization (Visit 2) and up to Week 26 (Visit 5) for the non-hemodynamic cohort and from 90 days prior to the baseline RHC (and LHC, if needed) qualifying for enrollment and up to Week 26 (Visit 5) for the hemodynamic cohort.
- Treatment with prostacyclin (epoprostenol), prostacyclin analogs (ie, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/Uptravi) within 90 days prior to randomization (Visit 2) and up to study treatment discontinuation.
- Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to baseline RHC (and LHC, if needed).
- Treatment with strong inhibitors of CYP2C8 (eg, gemfibrozil) within 14 days prior to randomization and up to 30 days after study treatment discontinuation.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint(s)

The primary efficacy endpoint of this study is the PVR at Week 20, assessed at rest, within 2–5 hours post-dose, expressed as percent of baseline PVR.

This endpoint has been selected as it is of high prognostic value in the treatment and management of CTEPH [Hoeper 2009] and because high preoperative values are indicative of a significant risk of surgical mortality [Dartevelle 2004].

6.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline in 6MWD to Week 26 (key secondary endpoint).
- TTCW (key secondary endpoint), where clinical worsening is defined (adapted from the CHMP definition [EMEA 2008]) as at least one of the following components confirmed by the CEC, when applicable:
  - All-cause death
  - Non-planned PH-related hospitalization
  - PH-related deterioration identified by at least one of the following:
    - Increase from baseline in WHO FC[4];
    - Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD[4];

[4] Confirmed by a second measurement performed on a different day within 14 days.

  - New or worsening of signs or symptoms of right heart failure, defined as a reported AE with one of the following preferred terms: "CTEPH", "pulmonary hypertension", "right ventricular failure", "right ventricular dysfunction" and "acute right ventricular failure".

- All-cause death or hospitalizations related to PH worsening.
- Improvement in WHO FC from baseline to Week 26.
- Change from baseline to Week 26 in Pulmonary arterial hypertension-symptoms and impact questionnaire (PAH-SYMPACT®) cardiopulmonary symptoms domain and cardiovascular symptoms domain.
- Change from baseline to Week 26 in Borg dyspnea index (BDI)/Borg CR10®.
- Change from baseline to Week 26 in NT-proBNP.

6.1.3 Other efficacy endpoints

The other efficacy endpoints of this study are:

- Changes in 6MWD, WHO FC and NT-proBNP from baseline to all regular collection timepoints up to the EDBT period.
- Change from baseline up to EOS, by visit, in exercise capacity, as measured by the 6MWD.
- Rate of hospitalizations up to the EDBT period.
- Mean number of hospital days for all-cause hospitalization.
- Mean number of hospital days related to PH worsening.
- Improvement in WHO FC from baseline up to EOS, by visit.
- Change from baseline to Week 26 in actigraphy-assessed daily life physical activity (DLPA
-).Change from baseline up to Week 39, by visit, in PAH-SYMPACT® scores (including cardiopulmonary symptoms domain, cardiovascular symptoms domain, physical impacts domain, and cognitive/emotional impacts domain).
- Change from baseline up to EOS, by visit, in BDI/Borg CR10® collected immediately at the end of each individual 6MWT.
- Change from baseline up to Week 52, by visit, in Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L).
- Change from baseline up to Week 52, by visit, in Work Productivity and Activity Impairment: General Health (WPAI©: GH) scores.
- Change from baseline to all regular collection timepoints up to the EDBT period in the Clinician Global Impression of Severity (CGI-S) scores and in the Clinician Global Impression of Change (CGI-C) scores.
- Change from baseline to Week 20 in other hemodynamic parameters (cardiac output [CO], cardiac index [CI] and mean right atrial pressure [mRAP]) measured at rest.

- Change from baseline to Week 20 in the number of low-risk criteria, defined as WHO FC I or II, 6MWD ≥440 m, NT-proBNP <300 ng/L and CI criteria ≥2.5 L/min/m^2 [Galiè 2016].

6.2 Safety endpoints

- Treatment-emergent AEs[5] up to 3 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].
- Serious adverse events (SAEs) up to 30 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].
- AEs leading to premature discontinuation of study treatment at each analysis time point [see Section 5.1.6.1].
- Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points during the study at each analysis time point [see Section 5.1.6.1].
- Treatment-emergent marked laboratory abnormalities up to 3 days after study treatment discontinuation as detailed in Appendix 2 at each analysis time point [see Section 5.1.6.1].
- Treatment-emergent AEs[5] of special interest (eg, hypotension, anemia, hyperthyroidism) up to 3 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 General information

The study visits are listed in Table 3, Table 4 and Table 5. For all visits, the subjects must be seen or called on the designated day with an allowed visit window indicated in Table 3, Table 4 and Table 5. A follow-up safety telephone call / visit must be performed 30 (+5) days after intake of the last dose of study treatment. 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.

In case of premature discontinuation of study treatment, the EDBT or the EOLT visit must take place as soon as possible and no later than 7 days after the last dose of study treatment. Subjects who prematurely discontinue study treatment or withdraw consent from further participation in the study for any reason will not be replaced.

[5] A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment start until 3 days after study treatment discontinuation), whether or not considered by the investigator as related to study treatment.

7.1.1 Screening/rescreening

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 subject participating in this study after adequate face-to-face explanation of the objectives, methods, and potential hazards of the study. The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to any study-related assessment or procedure.

Subjects who are in screening when the enrollment target has been met may still be randomized.

It is permitted to re-screen subjects once if the reason for non-eligibility was transient (eg, abnormal laboratory test, insufficient wash-out period of a forbidden medication, subject's condition changes). Informed consent [see Section 12.3] and all screening assessments must be repeated at the time of rescreening. If the screening V/Q scan, PA, CTPA, MRA and RHC (and LHC, if needed) were done as per timing requirements indicated in Sections 7.2.2 and 7.2.3.1.1, respectively, these do not need to be repeated.

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.

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

If any RHC (and LHC, if needed) is done at an unscheduled visit, this must be collected in the eCRF.

During the DB treatment or the PTOP period:

- an unscheduled visit must be performed within 14 days of the following occurring **at an on-site visit**:
    - Increase from baseline in WHO FC.
    - Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD.
- an unscheduled visit must be performed within 14 days of site knowledge in case of the following occurring **outside of a scheduled visit**:
    - Suspected clinical worsening, defined as i) any new AE suggestive of right heart failure or disease progression, and ii) any new evidence of a decrease in exercise capacity or increase in dyspnea.

- Any change in dose/initiation of new PH-specific therapies and/or up-titration of DB study treatment beyond Week 12 (when applicable).

In these cases, the following assessments must be performed: physical examination, vital signs (blood pressure, heart rate [HR]), weight, post-dose 6MWT/BDI or Borg CR10® and WHO FC. In addition, concomitant therapy and SAEs/AEs will be collected. Further assessments are performed at the discretion of the investigator.

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

Table 3 Double-blind treatment period: visit and assessment schedule

PERIODS	Name	SCREENING	DOUBLE-BLIND TREATMENT										
	Duration	At least 14 days and up to 60 days											
VISITS	Number	1	2	Titration phase	3	4	5	6	7	TC every 26 weeks[10]	Visit every 26 weeks[10]	EDBT	U1, 2, 3, etc.
	Name	Screening/ Rescreening	Randomization		Week 12	Week 20	Week 26	Week 39	Week 52	Week 65, 91, 117, etc.	Week 78, 104, 130, etc	Announced[11] or for premature EDBT within 7 days after last DB dose	Unscheduled visit[1]
	Time	Day −60 to Day −14	Day 1	Weekly from Week 1 to Week 11 (± 3 days)	Day 85 (± 7 days)	Day 141 (± 7 days)	Day 183 (± 7 days)	Day 274 (± 7 days)	Day 365 (± 7 days)	Day 456, 638, 820 etc. (± 7 days)	Day 547, 729, 911, etc. (± 7 days)		Any time
Informed consent		X											
Eligibility		X	X										
Medical history/ Demographics		X											
Previous/concomitant therapy		X	X	X	X	X	X	X	X	X	X	X	W
Physical examination*		X	X		X	X	X	X	X		X	X	W
Height		X											
Vital signs (BP, HR), Weight		X	X		X	X	X	X	X		X	X	W
Local 12-lead ECG		X							X			X	(X)
RHC (and LHC, if needed)		X[2]				X[3,4]							(X)
V/Q scan, PA, CTPA, MRA[5]		X											
Hematology and clinical chemistry**		X	X[6]		X	X	X	X	X		X	X	(X)
Serum pregnancy test**		X											(X)
Urine pregnancy test*			X	← monthly (±7 days) →									(X)
6MWT/BDI or Borg CR10®		X	X										
Post-dose 6MWT/BDI or Borg CR10®[3]					X	X	X	X	X		X	X	W

PERIODS	Name	SCREENING	DOUBLE-BLIND TREATMENT										
	Duration	At least 14 days and up to 60 days											
VISITS	Number	1	2	Titration phase	3	4	5	6	7	TC every 26 weeks[10]	Visit every 26 weeks[10]	EDBT	U1, 2, 3, etc.
	Name	Screening/ Rescreening	Randomization		Week 12	Week 20	Week 26	Week 39	Week 52	Week 65, 91, 117, etc.	Week 78, 104, 130, etc	Announced[11] or for premature EDBT within 7 days after last DB dose	Unscheduled visit[1]
	Time	Day −60 to Day −14	Day 1	Weekly from Week 1 to Week 11 (± 3 days)	Day 85 (± 7 days)	Day 141 (± 7 days)	Day 183 (± 7 days)	Day 274 (± 7 days)	Day 365 (± 7 days)	Day 456, 638, 820 etc. (± 7 days)	Day 547, 729, 911, etc. (± 7 days)		Any time
WHO FC		X	X		X	X	X	X	X		X	X	W
Actigraphy**		X	←	Every day, 24 hours per day			→						
PAH-SYMPACT®,[7]**		X	X		X	X	X	X					
EQ-5D-5L, WPAI©: GH**		X	X		X	X	X	X	X				
CGI-S			X		X	X	X	X	X		X	X	
CGI-C					X	X	X	X	X		X	X	
NT-proBNP**		X	X		X	X	X	X	X		X	X	(X)
Dose titration				☎[8]	iMTD								
DB Study treatment dispensing/return		–	X		X	X	X	X	X		X	X	
SAEs/AEs[9]		X	X	X	X	X	X	X	X	X	X	X	W

6MWT = 6-minute walk test; AE = adverse event; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®; BP = blood pressure; BPA = balloon pulmonary angioplasty; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; CT = computed tomography; CTPA = computed tomography pulmonary angiogram; DB = double-blind; ECG = electrocardiogram; eCRF = electronic Case Report Form; EDBT = End-of-Double-Blind-Treatment; EOS = end of study; EQ-5D-5L = Euro Quality of Life-5-Dimension-5-Level; FC = functional class; HR = heart rate; IDMC = Independent data management committee; iMTD = individual maximum tolerated dose; LHC = left heart catheterization; MRA = magnetic resonance angiography; NT-proBNP = N-terminal pro b-type natriuretic peptide; PA = pulmonary angiography; PAH-SYMPACT® = Pulmonary arterial hypertension symptoms and impact

questionnaire; PEA = pulmonary endarterectomy; RHC = right heart catheterization; SAE = serious adverse event; V/Q scan = ventilation/perfusion scan; WHO = World Health Organization; WPAI©: GH = Work Productivity and Activity Impairment Questionnaire: General Health. ☎ = telephone call.

[1] Unscheduled visits may be performed at any time during the DB treatment period. Assessments (marked with an '(X)' or 'W' in Table 3) are performed at the discretion of the investigator.

If the unscheduled visit is performed due to increase from baseline in WHO FC, deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD, suspicion of clinical worsening [as defined in Section 7.1.2], any change in dose, initiation of PH-specific therapies, or up-titration of DB study treatment beyond Week 12, the mandatory assessments to be performed are marked with a 'W'. If an RHC (and LHC, if needed) is done at an unscheduled visit, this information must be collected in the eCRF.

[2] RHC (and LHC, if needed) must have been performed at least 90 days after full anticoagulation and at least 90 days after last surgical (PEA) or interventional (BPA) treatment for subjects with persistent/recurrent CTEPH.

For the hemodynamic cohort, a historical RHC (and LHC, if needed) is allowed, provided it was performed within 30 days prior to Screening*, at least 90 days after last change in PH-specific therapies (ie, change in dose or initiation of new class of drugs) and as per guidance in Appendix 1.

For the non-hemodynamic cohort, historical RHC (and LHC, if needed) is allowed, provided it was performed within 6 months prior to Screening*.

If no historical results are available, RHC (and LHC, if needed) must be performed during the Screening period (as per guidance in Appendix 1 for the hemodynamic cohort).

* In case of rescreening in the hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit. In case of rescreening in the non-hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used.

[3] Assessment to be performed within 2–5 hours post-dose.

[4] Only for subjects in the hemodynamic cohort and must be done after the post-dose 6MWT.

[5] Performed in the 14-month period prior to randomization and after last surgical (PEA) and/or interventional (BPA) treatment for subjects with persistent/recurrent CTEPH [Section 7.2.2]. If no historical results are available, the assessments must be performed during the Screening period.

[6] If the results of the screening blood samples from the central laboratory are not available in time for randomization of the subject, an additional blood sample may be drawn to verify eligibility based on a local laboratory test.

[7] PAH-SYMPACT® questionnaire to be completed for the seven consecutive days following the visit at site (ie, starting the day following the visit day) for the symptom part, and on the seventh day of the symptoms diary data collection period, together with the symptom part (ie, in the evening) for the impact part.

[8] Scheduled telephone calls as per up-titration scheme [Section 5.1.3.1].

[9] All AEs and SAEs that occur after signing the Informed Consent Form and until the EOS, as defined in Section 8.1, must be reported [see also Section 9].

[10] After Week 52, the phone and on-site visits will be alternating every 13 weeks (~3 months).

[11] The EDBT visit occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.

* Assessment not collected in eCRF.

** Transferred electronically by an external service provider.

Table 4 Open-label treatment period: visit and assessment schedule

PERIODS	Name	TRANSITION	OPEN-LABEL TREATMENT					SAFETY FOLLOW-UP
	Duration		**At least until the DB period results release or up to a maximum of 26 weeks after the DB period results release**					**30 days**
VISITS[1]	**Number**	**EDBT**	**Titration phase**	**OL 1**	**OL 2**	***Visits every 26 weeks[7]***	**EOLT**	**Safety follow-up (Telephone call)**
	Name			**OL-Week 12**	**OL-Week 26**	***OL-Week 52, 78, 104, etc***		
	Time	**Announced[6]**	**Weekly from OL-Week 1 to OL-Week 11** (± 3 days)	**Day 85 after EDBT (± 7 days)**	**Day 183 after EDBT (± 7 days)**	***Day 365, 547, 729 after EDBT, etc (± 7 days)***	**Any time within 26 weeks of the DB period results release or for premature EOLT within 7 days after last OL dose**	**30 (+ 5) days after last OL dose**
Previous/concomitant therapy			X	X	X	X	X	X
Physical examination*				X	X	X	X	
Vital signs (BP, HR), Weight				X	X	X	X	
Hematology and clinical chemistry**				X	X	X	X	
Urine pregnancy test*			←			monthly (±7 days)	→	
Post-dose 6MWT/BDI or Borg CR10®[2]					X	X	X	
WHO FC					X	X	X	
Dose titration			☎[3]	iMTD				
OL Study treatment dispensing/return		X[4]		X	X	X	X	
SAEs/AEs[5]			X	X	X	X	X	X

6MWT = 6-minute walk test; AE = adverse event; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®; BP = blood pressure; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; DB = double blind; eCRF = electronic Case Report Form; EDBT = End-of-Double-Blind-Treatment; EOLT = End-of-Open-Label-Treatment; ,EOS = end of study; EQ-5D-5L = Euro Quality of life-5-Dimension-5-Level; FC = functional class; HR = heart rate; IDMC = Independent data management committee; iMTD = individual maximum tolerated dose; LHC = left heart catheterization; NT-pro BNP = N-terminal pro b-type natriuretic peptide; OL = open-label; PAH-SYMPACT® = Pulmonary arterial hypertension symptoms and impact questionnaire; PTOP-SFU = Post-treatment observation period-Safety follow-up; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization. ☎ = telephone call

[1] Unscheduled visits may be performed at any time during the OL treatment period. Assessments are performed at the discretion of the investigator. If any RHC (and LHC, if needed) is done at an unscheduled visit, this must be collected in the eCRF.

[2] Assessment to be performed within 2–5 hours post-dose.

[3] Scheduled telephone calls as per up-titration scheme [see Section 5.1.3.2].
[4] First OL dose to be taken on the evening of the EDBT visit or in the morning of the day after EDBT visit in case of qd regimen. [see Section 5.1.3.2].
[5] All AEs and SAEs that occur after first dose of OL study treatment and up to 30 days after study treatment discontinuation must be reported [see also Section 9].
[6] The EDBT visit occurs within 4 weeks after the end-of-double-blind period announcement ie within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.
[7] *ONLY FOR SUBJECTS WHO WERE TRANSITIONED TO THE OL TREATMENT EXTENSION PERIOD BEFORE IMPLEMENTATION OF THE AC-065B302 PROTOCOL AMENDMENT 2.*
* Assessment not collected in eCRF.
** Transferred electronically by an external service provider.

Table 5 Visit and assessment schedule for subjects entering the PTOP

PERIODS	Name		DOUBLE-BLIND PERIOD - OFF-TREATMENT[1] (after premature discontinuation of double-blind study treatment)								SURVIVAL FOLLOW-UP
VISITS	Number							TC every 26 weeks[8]	Visit every 26 weeks[8]	PTOP-EOS	SFU 1, 2, 3, etc
	Name	PTOP-SFU[2] (telephone call)	PTOP-Week 12	PTOP-Week 20	PTOP-Week 26	PTOP-Week 39	PTOP-Week 52	PTOP-Week 65, 91, 117, etc	PTOP-Week 78, 104, 130, etc	Announced[5]	Survival Follow-up
	Time	30 (+5 days) after last DB dose	Day 85 (± 7 days)	Day 141 (± 7 days)	Day 183 (± 7 days)	Day 274 (± 7 days)	Day 365 (± 7 days)	Day 456, 638, 820 etc. (± 7 days)	Day 547, 729, 911, etc. (± 7 days)		Yearly after study discontinuation until death or announcement[6]
Previous/concomitant therapy		X	X	X	X	X	X	X	X	X	
Physical examination*			X	X	X	X	X		X	X	
Vital signs (BP, HR), Weight			X	X	X	X	X		X	X	
Local 12-lead ECG							X			X	
Hematology and clinical chemistry**			X	X	X	X	X		X	X	
6MWT/BDI or Borg CR10®			X	X	X	X	X		X	X	
WHO FC			X	X	X	X	X		X	X	
Actigraphy**			← Every day, 24 hours per day →								
PAH-SYMPACT®, [3]**			X	X	X	X					
EQ-5D-5L, WPAI©: GH**			X	X	X	X	X				
CGI-S			X	X	X	X	X		X	X	
CGI-C			X	X	X	X	X		X	X	
NT-proBNP**			X	X	X	X	X		X	X	
SAEs/AEs[4]		X	X	X	X	X	X	X	X	X	
Survival											X[7]

6MWT = 6-minute walk test; AE = adverse event; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®, PTOP = Post-Treatment Observation Period; FC = functional class; SAE = serious adverse event; SFU = safety follow-up; WHO = World Health Organization.

[1] Depending on the time point of premature double-blind treatment discontinuation, the sequence and/or the applicability of visits may change. If one of the site visits falls within the time window of the premature EDBT visit [as defined in Section 5.1.10], only the assessments of the premature EDBT are to be performed.
[2] If the PTOP-SFU falls within the time window of any of the other PTOP visits, then the PTOP-SFU is combined with the corresponding PTOP site visit. In this case, the PTOP-SFU assessments are to be done in addition to the assessments of the respective visit.
[3] PAH-SYMPACT® questionnaire to be completed for the seven consecutive days following the visit at site (ie, starting the day following the visit day) for the symptom part, and on the seventh day of the symptoms diary data collection period, together with the symptom part (ie, in the evening) for the impact part.
[4] All AEs and SAEs that occur after signing the Informed Consent Form and until the EOS, as defined in Section 8.1, must be reported [see also Section 9].
[5] The PTOP-EOS visit occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.
[6] The end of the survival follow-up period for alive subjects will be announced and corresponds to the end-of-double-blind period announcement ie within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.
[7] Only for subjects who prematurely discontinue from DB study treatment and who disagree to continue to perform visits and assessments until the end of the PTOP, survival information will be collected yearly [see Section 7.2.3.9].
[8] After Week 52, the phone and on-site visits will be alternating every 13 weeks (~3 months).
* Assessment not collected in electronic Case Report Form.
** Transferred electronically by an external service provider.

7.2 Study assessments

The study assessments are listed in Table 3, 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)'. Mandatory assessments at an unscheduled visit due to increase from baseline in WHO FC, deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD, suspicion of clinical worsening, any change in dose, initiation of PH-specific therapies or up-titration of DB study treatment beyond Week 12 during the DB treatment period are marked with a 'W'.

All study assessments are performed by qualified study personnel (medical, nursing or specialist technical personnel) and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF. The following order of assessments is recommended:

- PRO completed at subject's home: PAH-SYMPACT®
- Investigator to complete CGI-S and CGI-C
- PROs: EQ-5D-5L and WPAI©: GH
- Safety assessments
- WHO FC
- 6MWT
- BDI or Borg CR10® immediately after completion of the 6MWT
- Blood samples for hematology and clinical chemistry tests and NT-proBNP (as applicable)
- RHC (and LHC, if needed) at rest, as applicable

If the Principal Investigator (PI) delegates any study procedure/assessment for a subject, eg, ECG, RHC (and LHC, if needed), V/Q scan, PA, CTPA, MRA, blood sampling to an external facility, he/she 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.

Evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the screening of the first subject. Evidence of equipment maintenance of other equipment must be available as per local requirements.

- Temperature measurement devices for study treatment storage area and freezer.
- RHC equipment.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all randomized subjects include: age, sex, race and ethnicity[6], weight and height, date of the initial CTEPH diagnosis, WHO FC, smoking status (never, former, current), and dates of the V/Q scan, PA, CTPA and/or MRA used to confirm the diagnosis of CTEPH.

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

For all screened subjects, the use of PH-specific therapies (ERA, PDE-5 inhibitors, riociguat), as well as the reason for not prescribing those are collected (not available, not reimbursed, contraindicated / not tolerated, other).

For subjects who failed screening, the following data will be recorded in the eCRF, if available: reason for screening failure, baseline data collected until confirmation of the screening failure (at a minimum, data that support the reason for screening failure).

7.2.2 Assessments for diagnosis of CTEPH and judgment of inoperability

A baseline RHC (and LHC, if needed) is mandatory for all subjects, as detailed in Section 7.2.3.1.1.

V/Q scan, PA, CTPA and MRA assessments are mandatory for the diagnosis of CTEPH and judgment of inoperability as follows [see also Section 4.1.1]:

- Subjects with inoperable CTEPH (ie, technically non-operable) will require a diagnosis of CTEPH **based on at least two** of these imaging assessments.
- Subjects with persistent/recurrent CTEPH after PEA and/or BPA will require a diagnosis of CTEPH **based on at least one** of these imaging assessments and a historical surgery & intervention report.

Historical results are accepted if the imaging assessment was performed within 14 months prior to randomization (Visit 2) and after last surgical (PEA) and/or interventional (BPA) treatment for subjects with persistent/recurrent CTEPH. If no historical results are available, the assessments must be performed during the Screening period.

Results of these imaging assessments will not be collected in the eCRF (except for the type and date of test[s]) but must be filed at site in the subject's file. In order to allow the AC to

[6] Race/ethnicity will be collected in the eCRF only where it is allowed.

confirm subject eligibility prior to randomization [see Section 4.1.1], the anonymized data (images and forms) will be transferred via a central image processing center to the AC.

Incidental findings unrelated to CTEPH identified by central reading will be communicated by the central image processing center to the investigator, who is responsible for taking appropriate action.

If the primary investigational site does not have the possibility to perform these imaging assessments, the sponsor could support the assessment at another specialized site [see Section 7.2]. The investigator at the primary site remains accountable for review and submission of V/Q scan, PA, CTPA and MRA data to the AC.

7.2.3 Efficacy assessments

7.2.3.1 Right heart catheterization (and left heart catheterization, if needed)

Hemodynamic data will be assessed during the RHC (and LHC, if needed) procedures. Detailed guidance is provided in Appendix 1.

For the hemodynamic cohort, the following hemodynamic parameters are to be collected in the eCRF: HR and peripheral systolic and diastolic blood pressure (sSAP / dSAP), PAWP (alternatively LVEDP when PAWP is not available or not reliable), mRAP, systolic / diastolic pulmonary artery pressures (sPAP / dPAP), CO and mixed venous oxygen saturation (SvO_2).

For the non-hemodynamic cohort, the following hemodynamic parameters are to be collected in the eCRF: HR and sSAP / dSAP , PAWP (alternatively LVEDP when PAWP is not available or not reliable), mRAP, sPAP / dPAP / mean pulmonary artery pressures (mPAP), CO, mixed venous oxygen saturation (SvO_2) and PVR. CI and total pulmonary resistance should be entered into the eCRF by the site if available.

If the primary investigational site does not have the possibility to perform an RHC (and LHC, if needed), the sponsor could support the assessment at another specialized site [see Section 7.2]. The investigator at the primary site remains accountable for review and submission of RHC (and LHC, if needed) data to the AC.

7.2.3.1.1 Baseline RHC (and LHC, if needed)

All subjects must have an RHC (and LHC, if needed), performed at least 90 days after full anticoagulation, available to evaluate eligibility.

For subjects with persistent/recurrent CTEPH after PEA and/or BPA, the RHC (and LHC, if needed) must be performed at least 90 days after last surgical (PEA) or interventional (BPA) treatment.

For the hemodynamic cohort, a historical RHC (and LHC, if needed) is allowed provided it was performed within 30 days prior to Screening*, at least 90 days after last change in PH-specific therapies (ie, change in dose or initiation of new class of drugs) and as per guidance in Appendix 1.

For the non-hemodynamic cohort, a historical RHC (and LHC, if needed) is allowed, provided it was performed within 6 months prior to Screening*.

If no historical results are available, an RHC (and LHC, if needed) must be performed during the Screening period (as per guidance in Appendix 1 for the hemodynamic cohort).

* In case of rescreening in the hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit. In case of rescreening in the non-hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used.

7.2.3.1.2 Week 20 RHC (and LHC, if needed)

At Week 20, an RHC (and LHC, if needed) is required for the assessment of the primary endpoint and will be conducted in approximately the first 90 randomized subjects that enroll in the hemodynamic cohort. The RHC (and LHC, if needed) must be performed following the post-dose 6MWD assessment (if applicable) and within 2–5 hours post-dose. The time of the study treatment morning dose intake will be recorded in the eCRF.

For the hemodynamic cohort, Week 20 RHC (and LHC, if needed) must be performed according to guidance detailed in Appendix 1.

An RHC (and LHC, if needed) performed at any unscheduled visit must be entered into the eCRF.

7.2.3.2 Exercise capacity

Exercise capacity will be measured by the 6MWT. The 6MWT is a non-encouraged test that measures the distance walked in 6 minutes (6MWD). It is performed as indicated in Table 3, Table 4 and Table 5.

Beginning with the morning of Visit 3, and at each visit thereafter, subjects must take the morning study treatment dose before any visit-related procedure. The post-dose 6MWT must be performed within 2–5 hours post-dose. The time of the study treatment morning dose intake will be recorded in the eCRF.

Guidelines on correct execution of the 6MWT are provided in Appendix 3.

Before study start, it must be verified whether the site can comply with the 6MWT study guidance [see Appendix 3]. If a 6MWT cannot be performed at a scheduled visit beyond Visit 2 or at an unscheduled visit, a reason must be provided (ie, clinical worsening or other).

The data related to 6MWT will be recorded in the eCRF.

7.2.3.3 Post-6MWT Dyspnea

The perception of dyspnea will be assessed by the BDI scale/Borg CR10 Scale® by each individual subject immediately after each 6MWT.

Subjects enrolled **before** implementation of the AC-065B302 protocol amendment 2 must continue using the **BDI scale in Appendix 4**.

Subjects enrolled **after** implementation of the AC-065B302 protocol amendment 2 must use the **Borg CR10 Scale® in Appendix 5**.

The perception of dyspnea will be collected in the eCRF.

7.2.3.4 WHO FC

WHO FC [Appendix 6] will be assessed as indicated in Table 3, Table 4 and Table 5.

WHO FC will be collected in the eCRF.

7.2.3.5 Daily life physical activity (DLPA)

The DLPA of subjects is assessed via an actigraphy device. The device is given to the subject at Visit 1 (Screening Visit), and the subject is instructed to wear the actigraphy device on the wrist of the non-dominant hand (ambidextrous subjects may wear it on either wrist) during the entire study, up to Week 26. Subjects are instructed on the use of the actigraphy device and accessories via a subject guide. Raw data will be uploaded automatically via Bluetooth or during charging of the actigraphy device as described in the subject guide.

To ensure DLPA data quality, the site and the SM will have access to compliance data through a web portal and via weekly subject reports displaying subject's adherence to DLPA assessment. Should corrective actions be necessary, the subject may be contacted from the site staff (eg, telephone call, text message).

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

The vendor will have raw data and derive datasets such as epoch dataset (per second or minute), DLPA daily summary dataset, and sleep dataset. Datasets will include relevant

parameters and will be transferred to the sponsor as described in the Data Transfer Agreement.

Subjects must return the actigraphy device to the site at the Week 26 / Visit 5. The devices will be returned to the vendor. Upon request, the subject will be provided with a report (on paper) summarizing the subject's individual activity levels during his/her participation in the study.

7.2.3.6 Clinical worsening

In case of suspicion of clinical worsening outside of a scheduled visit [see Section 7.1.2], any change in dose, initiation of PH-specific therapies, or up-titration of DB study treatment beyond Week 12 during the DB treatment period, an unscheduled visit must be performed as detailed in Table 3. Data related to study-specific assessments, any concomitant therapies and any SAEs/AEs will be recorded in the eCRF.

7.2.3.7 NT-proBNP

A blood sample for the analysis of NT-proBNP will be drawn as indicated in Table 3.

Details regarding blood sampling procedures, collection and shipment of the samples are described in the central laboratory manual.

7.2.3.8 Clinician reported outcomes

7.2.3.8.1 Clinician Global Impression of Severity (CGI-S)

The CGI-S is a six-point single item scale. The investigator/delegate will rate the overall severity of the participant's disease on the day of administration with responses of none, very mild, mild, moderate, severe or very severe.

The outcome of the CGI-S will be recorded in the eCRF.

7.2.3.8.2 Clinician Global Impression of Change (CGI-C)

The CGI-C is a seven-point single item scale. The investigator/delegate will rate the overall participant's change of the participant's disease since baseline with responses of very much better, moderately better, a little better, no change, a little worse, moderately worse or very much worse.

The outcome of the CGI-C will be recorded in the eCRF.

7.2.3.9 Survival follow-up

For subjects who prematurely discontinue DB study treatment and do not agree to continue to perform the visits and assessments until the PTOP-EOS visit, long-term survival information will be collected yearly until death or the time of end-of-double-blind period

[see Section 5.1.10]. Subject's vital status, ie, alive/dead/unknown (including last date known to be alive if unknown) as well as death information and concomitant PH-specific therapies when applicable will be collected in the eCRF.

7.2.4 Safety assessments

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

7.2.4.1 Physical examination

Physical examination at Screening includes the examination of the general appearance, heart, lungs, abdomen, skin, extremities, eyes, ears, nose, throat, neck (including thyroid), lymph nodes and nervous system. At subsequent visits, physical examination includes the examination of heart, lungs, abdomen, and extremities.

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

Information for all physical examinations must be included in the source documentation at the study site.

The date of the physical examination will be collected in the eCRF. Clinically relevant findings (other than those related to CTEPH) 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.

7.2.4.2 Vital signs

Vital signs will be assessed as indicated in Table 3 and Table 4.

SBP, diastolic blood pressure and radial pulse measurements will be measured in a supine or sitting position. It is recommended to allow the subject to rest for at least 5 minutes and to use the same device, same position (supine or sitting), same arm, same operator and appropriate cuff size throughout the study for each individual subject.

7.2.4.3 Weight and height

Height will be measured at Screening.

Body weight will be measured in indoor clothing but without shoes as indicated in Table 3 and Table 4.

7.2.4.4 Electrocardiogram assessment

A standard 12-lead electrocardiogram (ECG) will be performed as indicated in Table 3.

The ECG will be interpreted locally and stored at the site.

Clinically relevant ECG findings that are present prior to the initiation of study treatment must be documented in the Medical History section of the eCRF. Clinically relevant ECG findings found after the study treatment initiation that were not present at Screening or that worsened during the study must be reported as an AE [see Section 9.1.1] as appropriate.

7.2.5 Laboratory assessments

7.2.5.1 Type of laboratory

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

If the results from the central laboratory are not available in time for randomization of the subject, an additional blood sample may be drawn to verify eligibility 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 require recording of local laboratory results for the parameters described in Section 7.2.5.2 (with corresponding normal ranges) include hospitalization of the subject due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If central laboratory samples are lost or cannot be analyzed for any reason, the investigator will consider collecting an additional sample as soon as possible for repeat analysis, if deemed medically necessary.

Central laboratory reports will be sent to the investigator. In case of specific (predefined) laboratory abnormalities, the central laboratory will alert sponsor personnel and concerned site personnel. Alert flags that will trigger such notifications are displayed in Appendix 2.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate and filed with the hospital chart. 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 informed consent must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities detected after signing of informed consent must be reported as an AE or SAE as appropriate [see Section 9] and must be followed up 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.

7.2.5.2 Laboratory tests

The subjects do not need to be fasted prior to the laboratory tests.

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

Hematology

- Hemoglobin (SI Unit: g/L; conventional unit: g/dL)
- Hematocrit (SI Unit: L/L; conventional unit: %)
- Erythrocyte 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

- Alanine aminotransferase (U/L)
- Aspartate aminotransferase (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)
- Sodium, potassium (mmol/L)
- Glomerular filtration rate (mL/min/1.73m^2), using the Modification of Diet in Renal Disease formula
- Thyroid hormones:
  - Free tri-iodothyronine (T3) (SI unit: pmol/L; conventional unit: pg/dL)
  - Total T3 (SI unit: nmol/L; conventional unit: ng/dL)
  - Free thyroxin (T4) (SI unit: pmol/L; conventional unit: ng/dL)
  - Total T4 (SI unit: nmol/L; conventional unit: ng/dL)
  - Thyroid stimulating hormone (TSH; SI unit: mIU/L; conventional unit: µIU/dL)

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed at Screening.

Urine pregnancy tests will be performed at randomization and monthly thereafter. Urine pregnancy tests are either performed on-site during a scheduled visit or at home with the pregnancy test validated kit provided by the site. The results of the urine pregnancy tests will not be collected in the eCRF. Results of pregnancy tests will be documented in the subject's records (pregnancy test card). The date of the urine pregnancy test reported on the pregnancy card will be collected in the eCRF.

If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

7.2.6 Patient-reported outcomes

The following PRO instruments will not be administered to illiterate subjects and will not be administered to a subject when the instrument is not available in a language that can be easily understood and read.

7.2.6.1 PAH-SYMPACT® questionnaire

The PAH-SYMPACT® [Appendix 7] questionnaire is a PRO instrument that was developed by Actelion Pharmaceuticals Ltd [McCollister 2016]. This questionnaire has been developed and validated for use in PAH patients. The clinical presentation and manifestation of symptoms appear to be consistent across subgroups of pulmonary hypertension (eg, PAH and CTEPH) [Galiè 2016]. Therefore, it was considered that the PAH-SYMPACT® would be the most appropriate disease-specific instrument and is now being validated in CTEPH patients. Site staff will explain to the subjects that this questionnaire is applicable to their disease.

The PAH-SYMPACT® consists of two parts:

- The symptom part is completed for the seven consecutive days following the visit at site (ie, starting the day following the visit day).
- The impact part is completed once, on the seventh day of the symptoms diary data collection period, together with the symptom part (ie, in the evening).

The PAH-SYMPACT® will be administered as indicated in Table 3.

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

The PAH-SYMPACT® will be administered via a hand-held mobile device that subjects take home. Subjects will be trained on the mobile device by the site staff during Visit 1. Data will be transferred to an electronic database immediately upon completion of the questionnaire via a cellular connection to the vendor.

To ensure PAH-SYMPACT® data quality, the site and the SM will have access to compliance data through a web portal and will be informed by the vendor if the questionnaire has not been completed per protocol. Should corrective actions be necessary, subjects may be contacted by the site staff (eg, telephone call, text message).

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

At Week 52 / Visit 7, subjects must return the mobile device to the site. The devices will be returned to the vendor.

7.2.6.2 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcomes [Janssen 2013].

The EQ-5D-5L [Appendix 8] will be administered as indicated in Table 3. Each individual subject will enter their scores on an electronic device. Subjects will be trained on the electronic device by the site staff during Visit 1. The data from the electronic device will be collected by the vendor, who will send the results to the sponsor.

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

7.2.6.3 WPAI©: GH V2.0

The WPAI©: GH [Appendix 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.

The WPAI©: GH will be administered as indicated in Table 3. Each individual subject will enter their scores on an electronic device. The data from the electronic device will be collected by the vendor, who will send the results to the sponsor.

Written permission is neither required nor provided to researchers using the WPAI©: GH.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

Subjects who perform the EOS telephone call / visit are considered as study completers:

- For subjects who complete their study treatment up to the EOLT visit, the EOS visit corresponds to the safety telephone call which occurs 30–35 days after last OL dose.
- For subjects who prematurely discontinue the DB study treatment, the EOS visit corresponds to the last visit in the PTOP period, ie, the PTOP-EOS visit. It occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events [Section 10.6.3], or earlier following recommendation of the IDMC [Section 10.4] and sponsor's decision [Section 8.3].
- For subjects who prematurely discontinue the OL study treatment, the EOS visit corresponds to the safety telephone call (ie, 30–35 days after last OL dose).

Subjects who prematurely withdraw from the study, per Section 8.2, are not considered as study completers:

- For subjects who prematurely withdraw from the study, the EOS date is defined as the date of either death, last unsuccessful follow-up contact attempt, consent withdrawal, physician decision or sponsor decision, depending on the reason for study discontinuation.

8.2 Premature withdrawal from study

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

Subjects 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 subject 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 subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (eg, a visit by site personnel to the subject's home, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she 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 (subject, investigator, or sponsor personnel), must be recorded in the eCRF.

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

discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but will not be collected in the eCRF. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

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 subjects 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 subjects' interests.

In addition, if the investigator suspends or terminates 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 and SC.

8.4 Medical care of subjects after study completion

After the subject's study completion, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations. If indicated, the sponsor will provide subjects who completed the study and did not prematurely discontinue study treatment with OL study treatment until access to commercial selexipag is possible in this indication in the subject's country of residence, according to local regulatory requirements.

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 subject 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 study treatment initiation until 3 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.
- Abnormal assessments, eg, change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

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.

If the intensity of an AE worsens within the DB study period, the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required to be reported.

If there is a worsening in intensity for an ongoing AE occurring during the subsequent OL study period, this must be reported in the eCRF as a new AE with the onset date equal to the date of worsening.

The three categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

A mild, moderate or severe AE may or may not be serious [see Section 9.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

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

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 the study treatment administered DB or OL (as applicable) 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 after signing of informed consent and until the EOS, as defined in Section 8.1, must be recorded on specific AE pages of the eCRF.

9.1.5 Follow-up of adverse events

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.

AEs still ongoing beyond the EOS, as defined in Section 8.1, must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up

information obtained after the subject's EOS telephone call / visit will not be collected by the sponsor.

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

The following reasons for hospitalization are not considered SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (ie, planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, eg, hospitalization for coronary angiography in a subject 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 signing of informed consent and until the EOS, as defined in Section 8.1, must be reported on AE pages in the eCRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment.

9.2.3 Follow-up of serious adverse events

SAEs still ongoing beyond the EOS, as defined in Section 8.1, must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up

information obtained after the subject's EOS telephone call / visit must be reported to the sponsor but is not recorded in the eCRF.

9.2.4 After EOS

New SAEs occurring after the EOS, as defined in Section 8.1, 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 subject and whether or not this event is considered by the investigator to be related to study treatment.

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

The expectedness of an adverse reaction is determined by the sponsor in the Reference Safety Information (RSI) section provided in the most recent version of the IB. 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 (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject 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 subjects or partners of male subjects 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. Any subject who becomes pregnant during the study must discontinue further study treatment [see Section 5.1.11.5].

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 before the EOS, as defined in Section 8.1, must be reported as a separate AE in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.2.5. 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 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 a sponsor study treatment in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study treatment

- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study treatment
- Unexpected therapeutic or clinical benefit from use of a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a sponsor medicinal product (with or without patient exposure to the sponsor 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 CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

9.6 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs and study-specific examinations, as required) is monitored and reviewed on a continuous basis by the sponsor's CTT (in charge of ensuring subjects' safety as well as data quality). In addition, an IDMC is monitoring safety data [see Section 3.4.2]. 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 data may be shared with external experts.

10 STATISTICAL METHODS

This study implements an adaptive group-sequential design with early futility and/or efficacy stopping rules for PVR, 6MWD and TTCW in the DB treatment period. The timing of interim and final analyses is shown in Figure 3 and detailed in Section 5.1.6.1.

Conditional to positive outcome of the PVR results at analysis time point 1, all secondary efficacy endpoints will be evaluated at subsequent analysis time points according to the testing hierarchy [Section 10.3.1, Figure 4]. At final DB analysis (time point 4) and at final study analysis (time point 5), all endpoints will be summarized and analyzed with all available information.

All statistical analyses will be conducted by the sponsor or by a designated CRO supervised by the sponsor, with the exception of the analyses at time points 1, 2 and 3, which will be

conducted by the independent SSG for the IDMC, and by the independent submission team, if applicable.

Estimands, analyses, data displays, and algorithms to be used for data derivations will be fully detailed in the SAP.

The SAP will also include the definition of the protocol deviations and the link between protocol deviations and the analysis sets. The protocol deviations will be identified before interim and final analyses and before study closure.

Subgroup analyses, classifying subjects according to relevant demographic and baseline characteristics, will be further described in the SAP to evaluate efficacy and safety results.

The SAP will be finalized in advance of the planned IA.

10.1 Analysis sets

10.1.1 Screened Analysis Set

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

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received); and
- All available data are included.

10.1.3 Hemodynamic Set

The Hemodynamic Set (HES) comprises all randomized subjects in the hemodynamic cohort [Section 3.1]. In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received); and
- All available data are included.

10.1.4 Per-protocol Analysis Sets

Three Per-protocol Analysis Sets (PPS) are defined separately for PVR (PPS1), 6MWD (PPS2) and TTCW (PPS3). Each PPS comprises all subjects who received study treatment and who complied with the protocol sufficiently to be likely to exhibit the treatment effects. Criteria for sufficient compliance include exposure to study treatment, availability of

measurements and absence of important protocol deviations that have an impact on the treatment effect. The full list of criteria will be detailed in the SAP. Each PPS includes observations up to the occurrence of the specified protocol deviations. Additional specifications of the three PPS's are given below.

10.1.4.1 PVR Per-protocol Analysis Set

The PVR Per-protocol Analysis Set (PPS1) includes all subjects in the HES who do not have important protocol deviations that have an impact on treatment effect in PVR.

10.1.4.2 6MWD Per-protocol Analysis Set

The 6MWD Per-protocol Analysis Set (PPS2) includes all subjects in the FAS who do not have important protocol deviations that have an impact on treatment effect in 6MWD.

10.1.4.3 TTCW Per-protocol Analysis Set

The TTCW Per-protocol Analysis Set (PPS3) includes all subjects in the FAS who do not have important protocol deviations that have an impact on treatment effect in TTCW.

10.1.5 Safety Analysis Set

The Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment.

Subjects are evaluated according to the study treatment they have received (which may be different from the study treatment they have been randomized to):

- if a subject has taken at least one dose of selexipag, she/he is assigned to the selexipag treatment group;
- if a subject has taken only placebo, she/he is assigned to the placebo treatment group.

10.1.6 Selexipag-initiated Set

The Selexipag-initiated Set (SIS) analysis comprises all subjects initiated at any time during DB or OL treatment on selexipag. The baseline for this analysis set is the last assessment before selexipag initiation.

10.1.7 Usage of the analysis sets

Table 6 defines all analysis sets and their specific usage at all analysis time points. For decision making at analysis time point 1, PVR will be evaluated on the HES. All other efficacy analyses will be primarily evaluated on the FAS. The SIS will be used to evaluate subjects initiated at any time on selexipag. Safety endpoints will be primarily evaluated on the SAF.

If the study is stopped after an IA during the DB treatment period, the final DB analysis of all endpoints will be performed using all available data up to EDBT visit.

Table 6 Analysis sets and their usage at each analysis time point

Analysis Time point	Analysis	Analysis Set				
		FAS	**HES**	**PPS**	**SAF**	**SIS**
1	Final PVR		X	PPS1		
1	Exposure and safety				X	
1	Others*	X	X			
2	Interim 6MWD	X		PPS2		
2	Interim TTCW	X		PPS3		
2	Exposure and safety				X	
2	Others*	X				
3	Final 6MWD	X		PPS2		
3	Interim TTCW	X		PPS3		
3	Exposure and safety				X	
3	Others*	X				
4	Final TTCW	X		PPS3		
4	Final DB	X			X	
5	Final OL	X			X	X

* Demographic and baseline characteristics, medical history, previous and concomitant medications, efficacy endpoints other than PVR, 6MWD and TTCW.
The "X" indicates the analysis sets to be used for the main analyses for the respective endpoints and time points.
6MWD = 6-minute walk distance; DB = double-blind; FAS = Full Analysis Set; HES = Hemodynamic Set; OL = open-label; PPS = Per-protocol Analysis Set; PPS1 = PVR Per-protocol Analysis Set; PPS2 = 6MWD Per-protocol Analysis Set; PPS3 = TTCW Per-protocol Analysis Set; PVR = pulmonary vascular resistance; SAF = Safety Analysis Set; SIS = Selexipag-initiated Set; TTCW = Time to clinical worsening.

10.2 Variables

10.2.1 Primary efficacy variable

The primary efficacy variable is the percent of baseline PVR at Week 20 defined as:

(PVR (dyn.sec/cm^5) at Week 20 / PVR (dyn.sec/cm^5) at baseline) × 100

All observed data will be included. Imputations for missing data are specified in Section 10.3.2.2. PVR, mPAP, PAWP and CI as captured on the eCRF will only be displayed in listings. If the PAWP measurement is not available, then LVEDP will be used in the calculation of PVR. The results from the sponsor re-calculated PVR (in dyn.sec/cm^5) in the analysis dataset are used for analysis.

10.2.2 Secondary efficacy variables

One key secondary efficacy variable is change from baseline to Week 26 in 6MWD (in meters) as defined by:

(6MWD (m) at Week 26 − 6MWD (m) at baseline).

The baseline reference value (baseline) for the 6MWD is the distance obtained from the last 6MWT performed prior to or at randomization.

The other key secondary efficacy variable is TTCW, calculated from date of randomization to the date of onset of the first component event, where clinical worsening is defined (adapted from the CHMP definition [EMEA 2008]) as at least one of the following components confirmed by the CEC, when applicable:

- All-cause death
- Non-planned PH-related hospitalization
- PH-related deterioration identified by at least one of the following:
  - Increase from baseline in WHO FC*;
  - Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD*;
  - New or worsening signs or symptoms of right heart failure, defined as a reported AE with one of the following preferred terms: “CTEPH”, “pulmonary hypertension”, “right ventricular failure”, “right ventricular dysfunction” and “acute right ventricular failure”.

*Confirmed by a second measurement performed on a different day within 14 days.

Other secondary variables evaluated at Week 26 are:

- Improvement in WHO FC from baseline to Week 26

- Change from baseline to Week 26 in PAH-SYMPACT® cardiopulmonary symptoms domain and cardiovascular symptoms domain
- Change from baseline to Week 26 in BDI/Borg CR10®
- Change from baseline to Week 26 in NT pro-BNP

Another secondary endpoint is:

- All-cause death and hospitalizations related to PH worsening

Figure 4 defines the hierarchical testing strategy for the primary, key secondary and other secondary efficacy endpoints.

10.2.3 Other efficacy variables

- Changes in 6MWD, WHO FC and NT-proBNP from baseline to all regular collection timepoints up to the EDBT period.
- Change from baseline up to EOS, by visit, in exercise capacity as measured by the 6MWD.
- Rate of hospitalizations up to the EDBT period.
- Mean number of hospital days for all-cause hospitalization.
- Mean number of hospital days related to PH worsening.
- Improvement in WHO FC from baseline up to EOS, by visit.
- Change from baseline to Week 26 in actigraphy-assessed DLPA.
- Change from baseline up to Week 39, by visit, in PAH-SYMPACT® scores (including cardiopulmonary symptoms domain, cardiovascular symptoms domain, physical impacts domain, and cognitive/emotional impacts domain).
- Change from baseline up to EOS, by visit, in BDI/Borg CR10® collected immediately at the end of each individual 6MWT.
- Change from baseline up to Week 52, by visit, in EQ-5D-5L.
- Change from baseline up to Week 52, by visit, in WPAI©: GH scores.
- Change from baseline to all regular collection timepoints up to the EDBT period in the CGI-S scores and in the CGI-C scores.
- Change from baseline to Week 20 in other hemodynamic parameters (CO, CI and mRAP) measured at rest.
- Change from baseline to Week 20 in the number of low-risk criteria, defined as WHO FC I or II, 6MWD ≥440 m, NT-proBNP <300 ng/L and CI ≥2.5 L/min/m^2 [Galiè 2016].

Further details regarding endpoint definitions and analyses will be presented in the SAP.

10.2.4 Safety variables

- Treatment-emergent AEs up to 3 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].
- Serious adverse events (SAEs) up to 30 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].
- AEs leading to premature discontinuation of study treatment at each analysis time point [see Section 5.1.6.1].
- Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points during the study at each analysis time point [see Section 5.1.6.1].
- Treatment-emergent marked laboratory abnormalities up to 3 days after study treatment discontinuation as detailed in Appendix 2 at each analysis time point [see Section 5.1.6.1].
- Treatment-emergent AEs of special interest (eg, hypotension, anemia, hyperthyroidism) up to 3 days after study treatment discontinuation at each analysis time point [see Section 5.1.6.1].

AE data:

An AE is defined as any event that is recorded on the AE eCRF module, regardless of the onset date. An SAE is defined as any AE that is identified in the AE eCRF as serious. All coded AEs and SAEs will be considered as safety variables.

Treatment-emergent AEs are those with onset date/time ≥ start date/time of study treatment and ≤3 days after study treatment discontinuation.

Treatment-emergent AEs of special interest with onset date/time ≥ start date/time of study treatment and ≤3 days after study treatment discontinuation will also be tabulated.

Laboratory data:

Laboratory analyses are based on data received from the central laboratory. All transferred central laboratory data are considered regardless of whether they correspond to scheduled or unscheduled assessments.

‘Baseline laboratory test’ refers to the latest laboratory test performed prior to the start of study treatment. Missing baseline values are imputed using the median of the corresponding baseline test from all subjects with non-missing baseline values.

‘EOT laboratory test’ refers to the laboratory test performed at the EOT visit. If no laboratory data are available for the EOT visit, the results of the latest available post-baseline laboratory tests performed prior to EOT are used for the analysis.

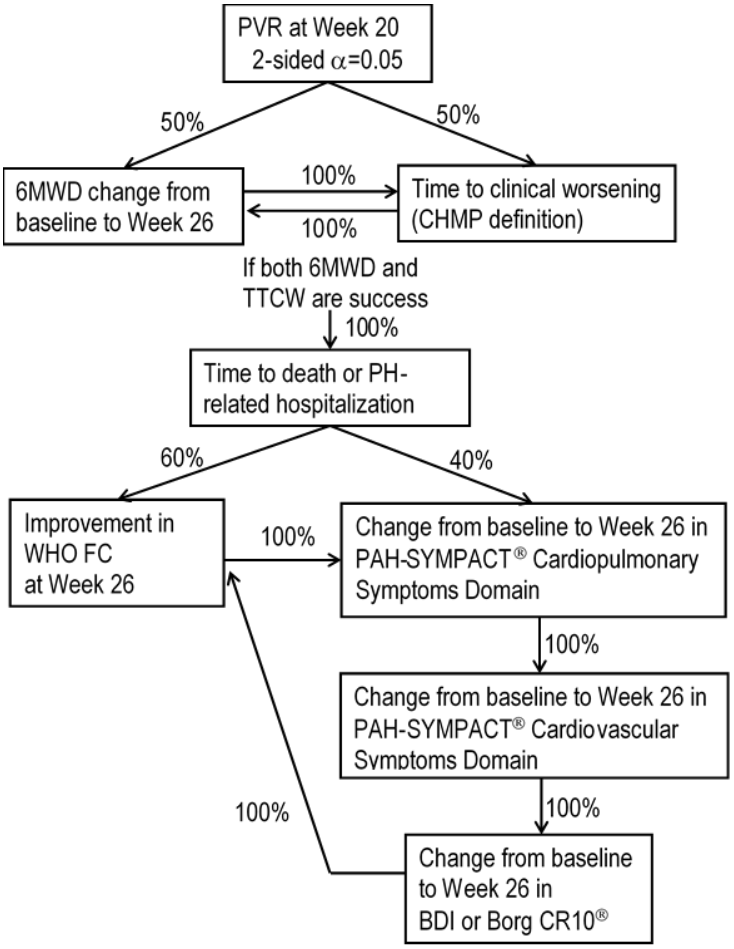
Treatment-emergent marked laboratory abnormalities up to 3 days after last study treatment intake will be considered.

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

A graphical testing strategy [Bretz 2009] will be implemented, controlling the family-wise error rate (FWER) at a two-sided significance level of α = 5% for the primary and secondary efficacy endpoints [Figure 4].

Figure 4 Testing strategy for primary and secondary endpoints (two-sided type I error rate, α = 5%)



6MWD = 6-minute walk distance; BDI = Borg dyspnea index; Borg CR10®= Borg category-ratio 10 Scale®; CHMP = Committee for Medicinal Products for Human Use; PAH-SYMPACT®= Pulmonary Arterial Hypertension Symptoms and Impact®; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TTCW = Time to clinical worsening; WHO FC = World Health Organization functional class.

At analysis time point 1, the primary endpoint PVR will be tested in the HES at a full two-sided alpha of 5%. Failure to meet success on the primary endpoint will lead to termination of the study for futility, as no remaining alpha is available to formally test secondary endpoints.

If the test of PVR is statistically significant at 5% alpha, then the study will continue, and the alpha will be split initially 50%:50% between 6MWD and TTCW following the weighted Bonferroni-Holm method [Holm 1979]. If the test of either 6MWD or TTCW is statistically significant at 2.5% alpha at any time point, then the other endpoint (TTCW or 6MWD) can be re-tested at 5% alpha. Only when both 6MWD and TTCW reach statistical significance, can the tests of the remaining secondary efficacy endpoints in the hierarchy be formally performed at the respective significance level at analysis time point 4. The formal testing process will stop when a test is not statistically significant at the respective significance level. Success on a particular endpoint may only be claimed if all endpoints in the hierarchy above this particular endpoint resulted in success.

There are four analysis time points during the DB treatment period. The applicability of analysis time points for the primary and secondary endpoints is summarized in Table 7.

Table 7 Analysis time points of the primary and secondary efficacy endpoints during the double-blind treatment period

Hierarchical order	**Endpoint**	**Time point 1** (90 subjects in HES completing 20 weeks)	**Time point 2** (160 subjects completing 26 weeks)	**Time point 3** (All subjects completing 26 weeks)	**Time point 4** (All subjects completing EDBT visit)
1	PVR at Week 20	X			
2a	6MWD at Week 26		X	X	
2b	TTCW		X	X	X
3	Time to death or PH-related hospitalization				X
4a	Improvement in WHO FC at Week 26				X
4b	Change from baseline to Week 26 in PAH-SYMPACT® Cardiopulmonary Symptoms Domain				X
5	Change from baseline to Week 26 in PAH-SYMPACT® Cardiovascular Symptoms Domain				X
6	Change from baseline to Week 26 in BDI or Borg CR10®				X

6MWD = 6-minute walk distance; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®; DB = double-blind; EDBT = End-of-Double-Blind-Treatment; HES = Hemodynamic set; FC = Functional class; PAH-SYMPACT® = Pulmonary arterial hypertension symptoms and impact questionnaire; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TTCW = time to clinical worsening; WHO = World Health Organization.The "X" indicates the applicable analysis time point(s) for the primary and secondary endpoints.

For the repeated analysis of 6MWD at the two analysis timepoints, the Hwang, Shih and DeCani (HSD)'s error spending function with parameter $\gamma = -4$ [Hwang 1990] will be applied [Section 10.4].

At the IA, the information fraction is the ratio of the number of subjects included in the IA to the target sample size 280 [Section 10.4].

For the repeated analysis of TTCW on the three analysis timepoints, the O'Brien and Fleming (OF) type error spending function [Lan 1983] will be applied [Section 10.4].

At each IA, the information fraction is the ratio of the number of events included in the IA to the target number of events 148 [Section 10.4].

The chance of both key secondary endpoints to be significant at an IA is considered to be low, therefore formal testing of all other secondary efficacy endpoints will be performed only at analysis time point 4, if applicable.

Details on the statistical analysis are given in the SAP. Guidelines for premature study termination are defined in Section 10.4 and the IDMC charter.

10.3.2 Analysis of the primary efficacy variable

At analysis time point 1, the PVR endpoint will be tested on the HES at two-sided alpha of 5%. Failure to meet success on the primary endpoint will lead to termination of the study for futility, as no remaining alpha is available to formally test secondary endpoints.

10.3.2.1 Hypotheses and statistical model

The hypotheses for the PVR endpoint are formulated in terms of geometric mean of percent of baseline PVR at Week 20 in subjects treated with selexipag versus placebo:

$$H_0: GM_{selexipag} = GM_{placebo}$$

$$H_A: GM_{selexipag} \neq GM_{placebo}$$

where:

$GM_{selexipag}$ and $GM_{placebo}$ are the geometric means of percent of baseline PVR at Week 20 for subjects treated with selexipag and placebo, respectively.

The PVR endpoint will be tested by means of an analysis of covariance (ANCOVA) model on the $\log_e$ transformed percent of baseline PVR at Week 20 (including imputed values). Model covariates will include randomized treatment, stratification factors (PH-specific therapies and CTEPH population) and the $\log_e$-transformed baseline PVR value. The resulting arithmetic mean and 95% CL of the natural logarithm of the ratio: PVR at Week 20 / PVR at baseline will be inversely transformed using the exponential function

and multiplied by 100 to provide the geometric mean of the ratio and corresponding 95% CL, expressed as a percent, by treatment group.

10.3.2.2 Handling of missing data

Imputation methods for the primary endpoint, PVR at Week 20 expressed as percent of baseline PVR, will be specific to the reason for missing data.

The baseline reference value for PVR is based on the last RHC (and LHC, if needed) performed prior to randomization, as defined in Section 7.2.3.1.1.

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

1. If PAWP and LVEDP are missing both at baseline and post-baseline, the missing PAWP is imputed using the median of all values observed at the respective time point in all subjects from the same randomized treatment group.
2. If PAWP and LVEDP are missing either at baseline or at post-baseline, the available PAWP for the subject is used as a substitute for the missing PAWP.

In the case of a missing PVR value at Week 20, the last available post-baseline value obtained before Week 20 is carried forward. It is assumed that this will mainly occur in subjects who have an unscheduled RHC (and LHC, if needed) performed at the time of a PH-related disease progression before Week 20. This imputation will be performed except in the following cases:

- If a subject dies without a Week 20 value, then the Week 20 PVR is imputed using the largest percent deterioration of baseline PVR at Week 20 among all subjects in the same treatment group.
- If the subject is alive and does not have a post-baseline value, the 50^{th} percentile of the percent of baseline PVR at Week 20 from all subjects in the same treatment group will be used to impute the Week 20 PVR value.

All observed values will be used to derive the imputed values.

If available, the RHC (and LHC, if needed) at the time of progression / treatment discontinuation is used for the primary analysis.

The main analysis will be carried out as described above on the HES. Absolute values at baseline and at Week 20 as well as absolute changes from baseline to Week 20 in PVR will be summarized using descriptive statistics for continuous variables. From the ANCOVA model, PVR at Week 20 expressed as a percent of baseline will be summarized by treatment group using covariate-adjusted geometric means and corresponding 95% two-sided CL. The between-group ratio of geometric means with corresponding 95% two-sided

CL and p-value will be displayed for the placebo-corrected treatment effect. Additionally, the median percent change of the treatment effect and corresponding 95% CL will be displayed.

10.3.2.3 Supportive/sensitivity analyses

Sensitivity analyses will be conducted using alternative imputation rules on the primary endpoint data to assess the imputation assumptions of the main statistical analysis. These analyses will be outlined in the SAP.

A sensitivity analysis on PPS1 will be carried out to assess the robustness of the results of the main statistical analysis against protocol deviations leading to exclusion from the PPS1.

Further details will be included in the SAP.

10.3.3 Analysis of secondary efficacy variable(s)

Secondary efficacy variables and their analyses are described below, using analysis sets as specified in Table 6 and at analysis timepoints as specified in Table 7. All secondary efficacy variables will be sequentially tested in a graphical hierarchical approach [Bretz 2009] with alpha spent at different time points according to the specified error spending functions [as per Section 10.3.1]. The null hypothesis of a secondary efficacy endpoint is formally rejected if and only if the main analysis of that endpoint and all main analyses of preceding secondary efficacy endpoints result in rejection of the respective null hypotheses. This procedure preserves the family-wise type I error rate to the overall assigned two-sided alpha of 5% for the primary and secondary efficacy endpoints [Figure 4].

For each secondary endpoint, a repeated two-sided $(1-\alpha^*)\%$ CL for treatment effect will be presented at each applicable analysis time point (where α^* denotes the alpha level allocated to the respective endpoint). For the final analysis, the adjusted p-value, two-sided $(1-\alpha^*)\%$ CL and the corresponding median unbiased estimate for the treatment effect will be presented. If formal testing is not allowed, the presented p-value will be for exploratory purposes only.

- Change from baseline to Week 26 in 6MWD
  The hypotheses are formulated in terms of mean difference in the 6MWD change from baseline to Week 26 in subjects treated with selexipag versus placebo:

$$H_0: \mu_{selexipag} = \mu_{placebo}$$

$$H_A: \mu_{selexipag} \neq \mu_{placebo}$$

where:

$\mu_{selexipag}$ and $\mu_{placebo}$ are the means in the change from baseline to Week 26 for subjects randomized to selexipag and placebo, respectively. The analysis will be an ANCOVA including treatment group, baseline 6MWD and all stratification factors as covariates. Least squares estimates for each treatment group (mean and 95% CL) and for the placebo-corrected treatment effect (means, $(1-\alpha^*)\%$ CL, and the corresponding p-value) will be displayed. Depending on the results of the testing hierarchy specified in Figure 4, this endpoint will be tested at analysis time points 2 and 3 [see Table 7]. The allocated α* will be either 2.5% or 5%.

- TTCW, where clinical worsening is defined (adapted from the CHMP definition [EMEA 2008]) as at least one of the following components confirmed by the CEC, when applicable:
  - All-cause death
  - Non-planned PH-related hospitalization
  - PH-related deterioration identified by at least one of the following:
    - Increase from baseline in WHO FC*;
    - Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD*;
    - New or worsening signs or symptoms of right heart failure, defined as a reported AE with one of the following preferred terms: "CTEPH", "pulmonary hypertension", "right ventricular failure", "right ventricular dysfunction" and "acute right ventricular failure".

  *Confirmed by a second measurement performed on a different day within 14 days.

The TTCW will be calculated from the date of randomization to the date of onset of the first component event. The null hypothesis is that there is no difference between selexipag and placebo for the distribution of time to the first CHMP-defined clinical worsening event. A two-sided stratified (for the stratification factors) log-rank test will be applied and the resulting p-value will be presented. Kaplan-Meier estimates with 95% CL for the survival functions will be provided for each treatment group. The hazard ratio will be estimated with two-sided $(1-\alpha^*)\%$ CL using a Cox model, including treatment group and all stratification factors as covariates. The frequency of each component event will also be presented. Depending on the results of the testing hierarchy specified in Figure 4, this endpoint will be tested at analysis time points 2, 3 and 4 [see Table 7]. The allocated α* will be either 2.5% or 5%.

- All-cause death or hospitalizations related to PH worsening (confirmed by the CEC)

The main analysis will be performed for the time from randomization to the first event among all-cause death or hospitalizations related to PH worsening that is confirmed by the CEC. The null hypothesis is that there is no difference between selexipag and placebo for the distribution of time to the first event among all-cause death or hospitalizations related to PH worsening. A two-sided stratified (for the stratification factors) log-rank test will be applied and the resulting p-value will be presented. Kaplan-Meier estimates for the survival functions will be provided together with two-sided 95% CL for each treatment group. The hazard ratio will be estimated with two-sided 95% CL using a Cox model, including treatment group and all stratification factors as covariates. The frequency of each component event will also be presented. Depending on the results of the testing hierarchy specified in Figure 4, this endpoint will be tested at analysis time point4 [see Table 7].

A supportive analysis will be performed on the rate of all-cause death or hospitalizations related to PH worsening. The null hypothesis is that there is no difference between selexipag and placebo in the hospitalization rate per 100-subject years, calculated by dividing the total number of all-cause death or hospitalizations related to PH worsening by the cumulative exposure of all subjects in each treatment arm. A negative-binomial regression model including treatment group and all stratification factors as covariates and with over-dispersion will be used to analyze the data. The different durations of follow-up time across subjects will be considered in the offset variable. This distribution assumes that each subject has recurrent hospitalizations related to PH worsening / death according to an individual-specific Poisson event rate, and that the Poisson rates vary according to a gamma distribution. The adjusted rate ratio, two-sided 95% CL and p-value will be provided. Depending on the results of the testing hierarchy specified in Figure 4, this endpoint may be tested at the same time as the main analysis time point (analysis time point 4).

- Improvement in WHO FC at Week 26

Improvement from baseline to Week 26 in WHO FC is defined as decrease in FC as compared to WHO FC at baseline. Subjects in FC I at baseline are excluded from the analysis as, by definition, their FC cannot be improved.The null hypothesis of same probabilities for improvement for selexipag and placebo will be tested by a Cochran-Mantel-Haenszel test adjusted by WHO FC at baseline, treatment and stratification factors. The common odds ratio with 95% CL will be estimated, provided there is no clear evidence against a common odds ratio across the strata (evaluated by the Breslow-Day test). Depending on the results of the testing hierarchy specified in Figure 4, this endpoint will be tested at analysis time point 4 [see Table 7] with total two-sided significance level $\alpha^* =$ 3% or 5%. The point estimate with two-sided $(1 - \alpha^*)\%$ CL and p-value for the treatment effect will be presented.

- Change from baseline to Week 26 in PAH-SYMPACT® cardiopulmonary symptoms domain and cardiovascular symptoms domain

Absolute change from baseline to Week 26 in each of the PAH-SYMPACT® symptoms domain scores is defined as:

(Score at Week 26 − Score at baseline)

For each score, the null hypothesis is that there is no difference between selexipag and placebo in the mean change from baseline to Week 26. The change from baseline to Week 26 in each PAH-SYMPACT® score will be analyzed by means of an ANCOVA model and will include treatment, baseline score value and stratification factors as covariates. Least squares estimates for each treatment group will be displayed with means and 95% CL. Responder analyses will also be implemented on PAH-SYMPACT® scores and will be defined in the SAP. Depending on the results of the testing hierarchy specified Figure 4, each score may be tested at analysis time point 4 [see Table 7] with total two-sided significance level $\alpha^* = 2\%$ or 5%. The mean with two-sided $(1 - \alpha^*)\%$ CL and p-value for the treatment effect will be presented.

- Change from baseline to Week 26 in BDI/Borg CR10®

Absolute change from baseline to Week 26 in BDI/Borg CR10® is defined as:

BDI/Borg CR10® at Week 26 − BDI/Borg CR10® at baseline.

The null hypothesis is that there is no difference between selexipag and placebo in the mean change from baseline to Week 26. The changes will be analyzed by means of an ANCOVA model and will include treatment, baseline index value and stratification factors as covariates. Least squares estimates for each treatment group will be displayed with means and 95% CL. Depending on the results of the testing hierarchy specified Figure 4, this endpoint may be tested at analysis time point 4 [see Table 7] with total two-sided significance level $\alpha^* = 2\%$ or 5%. The mean with two-sided $(1 - \alpha^*)\%$ CL and p-value for the treatment effect will be presented.

10.3.3.1 Handling of missing data

For the key secondary efficacy endpoint 6MWD, the following rules will be applied.

The Week 26 value is the one identified for the Week 26 analysis time window, as defined in detail in the SAP. The handling of missing data will be detailed in the SAP, which will be finalized before analysis time point 1. Imputation will be carried out as follows:

For subjects without any 6MWD available at Week 26, the following main imputation algorithm is applied:

- Rule 1: For subjects unable to walk at Week 26, a zero (0) is imputed for 6MWD at Week 26. Note: For subjects unable to walk due to clinical worsening at scheduled visits, 0 m is entered in the eCRF. This includes:
  - subjects who died without any visit performed in the Week 26 analysis time window (see SAP); and
  - subjects for whom the Week 26 visit corresponds to an unscheduled visit and were unable to walk for PH-related reasons (ie, the reason is coded as 'clinical worsening').
- Rule 2 (if Rule 1 does not apply): the second-lowest observed 6MWD value at Week 26 in the same analysis set (FAS), according to treatment group, is imputed.

Concerning the other key secondary endpoint TTCW, for subjects who have not experienced any event by the respective analysis cut-off date, their time will be right censored at the earliest date of the following: EDBT visit, the last PTOP visit, last contact, or analysis cut-off.

Additional sensitivity analyses may be described in the SAP, as well as imputations for other secondary variables.

10.3.4 Analysis of the safety variable(s)

10.3.4.1 Adverse events, serious adverse events, deaths and premature discontinuation of study treatment

All AEs and SAEs are coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

Individual subject listings of all collected AEs will be provided by treatment group. The frequency and the crude incidence of subjects who experienced treatment-emergent AEs until 3 days after last study treatment intake will be tabulated by system organ class (SOC), individual preferred terms within each SOC and by treatment group (in descending order according to the incidence in the investigational study treatment group).

Treatment-emergent AEs occurring up to 3 days after last study treatment intake will also be tabulated by severity and by relationship to study treatment and for selected subgroups, eg, gender and age (18–65 years, older than 65 years).

AEs leading to permanent discontinuation of study treatment will be listed and summarized similarly to AEs.

SAEs occurring up to 30 days after last study treatment intake will be listed and summarized similarly to AEs, separately for treatment-emergent SAEs and SAEs occurring

before study treatment initiation (only those related to study-mandated procedures) and after EOS.

Reasons for treatment-emergent deaths occurring up to 3 days after last study treatment intake will be listed and summarized similarly to AEs. Deaths occurring before study treatment initiation (only those related to study-mandated procedures) or more than 3 days after last study treatment intake will be listed separately by treatment group.

Reasons for premature discontinuation of study treatment will be listed and summarized by frequency tables. Individual subject listings will be provided by treatment group. Discontinuations will be tabulated overall and for the first 6 and 12 months of DB treatment.

10.3.4.2 Laboratory parameters

The frequency of subjects who experienced treatment-emergent marked laboratory abnormalities up to 3 days after study treatment discontinuation will be tabulated for each laboratory parameter by treatment group at each analysis time point.

Values of numeric laboratory parameters will be transformed to respective standard units for summary statistics (mean, median, standard deviation [SD], first and third quartiles, minimum and maximum) tabulated by treatment group for both the absolute values and the changes from baseline.

Individual subject listings will be provided by treatment group.

The sponsor's internal guidelines will be used for definition of marked laboratory abnormalities and for the standardization of numeric values obtained from different laboratory and/or using different normal ranges.

10.3.4.3 Vital signs and body weight

Vital signs (blood pressure and HR) and body weight will be summarized by tabulating mean, median, SD, first and third quartiles, minimum and maximum by treatment group for both the absolute values and the changes from baseline.

Individual subject listings will be provided by treatment group.

10.3.5 Subgroup analyses

Subgroup analyses will be conducted to assess consistency of results on the primary endpoint (according to the ANCOVA method described in Section 10.3.2) and selected secondary endpoints, based on the following baseline characteristics:

- Stratification factor 1: PH-specific therapies (one versus two versus naive)

- Stratification factor 2: CTEPH population (inoperable [with or without BPA] versus persistent/recurrent after PEA [including PEA followed by BPA])
- Participation in the hemodynamic cohort
- Gender
- Race (as defined in the SAP)
- Geographic region (as defined in the SAP)

An additional analysis of the primary and selected secondary endpoints will be conducted by dose group (low [200–400 µg bid], medium [600, 800 and 1000 µg bid] and high [1200, 1400 and 1600 µg bid]).

10.4 Interim analysis

As specified in Section 5.1.6.1, there are three IA time points during the DB treatment period.

At analysis time point 1, the analysis of the primary efficacy endpoint PVR will be conducted on the HES. If the analysis of PVR is statistically significant, the study will proceed as planned; otherwise, the study will be terminated. The IDMC will review the results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC.

At analysis time point 2, unblinded interim analyses for 6MWD and TTCW will be conducted on the FAS. If both 6MWD and TTCW are futile, then the study will be terminated prematurely. If at least one of 6MWD and TTCW is statistically significant, the study will be terminated due to overwhelming efficacy and subject recruitment will be stopped, but subjects already enrolled will remain on DB treatment as planned until all subjects have completed Week 26 assessments or prematurely discontinued from the study. Otherwise, the study will proceed as planned. The IDMC will review the results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC.

At analysis time point 3, an unblinded final analysis for 6MWD and an unblinded IA for TTCW will be conducted on the FAS. If 6MWD is not statistically significant and TTCW is futile, then the study will be terminated prematurely. If at least one of 6MWD and TTCW is statistically significant, the study will be terminated due to overwhelming efficacy. Otherwise, the study will proceed as planned. The IDMC will review the results and make corresponding recommendations in line with the IDMC charter. The independent SSG will make unblinded results available to the IDMC.

For 6MWD, the HSD error spending function with parameter $\gamma = -4$ [Hwang 1990] will be implemented to control the overall allocated two-sided significance level, α. With

information fraction (IF) at Stage i, for $i = 1, 2$, based on number of subjects at that stage, n_i, relative to the total sample size $n_2 = 280$, i.e. $t_i = n_i/n_2$, the HSD(-4) error spending function is:

$$\alpha_{HSD}(t_i) = \alpha \frac{1 - \mathrm{e}^{-\gamma t_i}}{1 - e^{-\gamma}} = \alpha \frac{1 - \mathrm{e}^{4t_i}}{1 - \mathrm{e}^{4}}$$

For TTCW, the overall allocated two-sided significance level, α for analyses at different analysis timepoints will be spent according to the OF-type error spending function [Lan 1983]. With IF at Stage i, for $i = 1, 2, 3$, based on the number of observed events at that stage, d_i, relative to the total number of required events, i.e. $t_i = d_i/d_3$, the OF-like error spending function is:

$$\alpha_{OF}(t_i) = 4\left[1 - \Phi\left(\frac{z_{1-\alpha/4}}{\sqrt{t_i}}\right)\right]$$

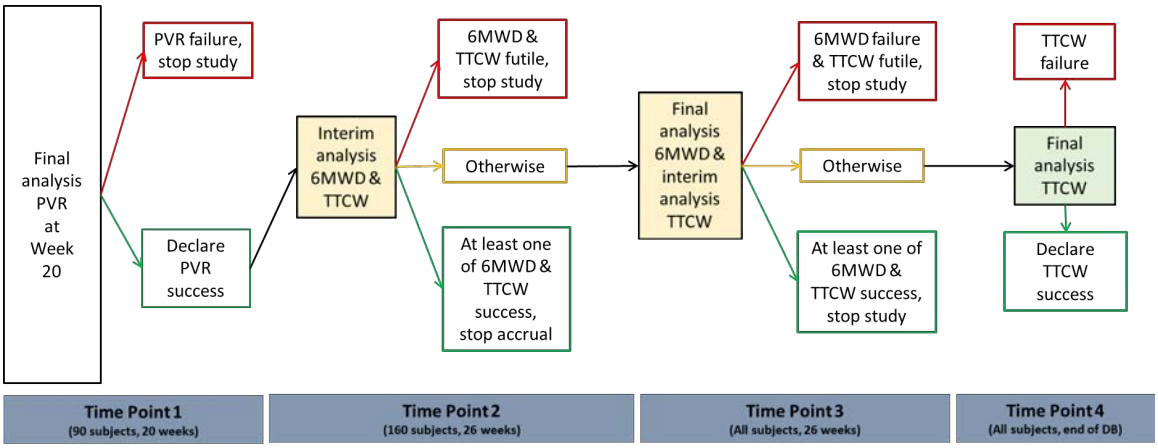
where $d_3 = 148$, Φ is the standard normal cumulative density function and z_x is the xth quantile of the standard normal distribution.

The end of DB period could occur and will be announced at different time points due to the following reasons:

Timepoint	Reason
1	Interim stop for futility due to failure of PVR
2	Interim stop for futility of both 6MWD and TTCW Interim stop (accrual) for efficacy if at least one of 6MWD and TTCW is successful
3	Interim stop for failure of 6MWD and futility of TTCW Interim stop for efficacy if at least one of 6MWD and TTCW is successful The required 148 clinical worsening events have been observed
4	The required 148 clinical worsening events have been observed
Throughout the study	IDMC recommendation Sponsor's decision

Detailed guidelines for interim decision-making are further described in the IDMC charter. Figure 5 describes the decision-making flow.

Figure 5 Flow of decision-making.



6MWD = 6-minute walk distance; DB = double-blind; PVR = pulmonary vascular resistance; TTCW = time to clinical worsening.

For secondary endpoints other than 6MWD and TTCW, formal testing will be performed only at analysis time point 4, if applicable and the two-sided significance level, α will be spent according to Figure 4.

If the study is stopped early at an interim time point, a supportive DB wrap-up analysis will be performed using all available data collected up to the EDBT visit.

10.5 Double-blind and open-label analyses

If the study is not stopped early for futility or efficacy at analysis time points 1, 2, or 3, the study will continue and blinding will be maintained until all subjects have completed DB treatment. Once all subjects complete DB treatment, they are enrolled in the OL period of the study and offered OL selexipag. At the final DB analysis (analysis time point 4), all secondary endpoints will be evaluated and reported in full in a DB Clinical Study Report (CSR). The analyses will be carried out on the analysis sets as defined in Section 10.1.

At the final study analysis (analysis time point 5), the data from all subjects enrolled in the OL extension period will be summarized and reported. Additionally, selected analyses will be carried out on the SIS, as defined in the SAP.

10.6 Sample size

The study will consist of two cohorts: approximately the first 90 subjects will be randomized in the hemodynamic cohort, targeting the primary endpoint of PVR. The remaining subjects will be randomized to enrich information on all secondary endpoints.

If subject enrollment is not terminated for efficacy or futility at analysis time points 1 or 2, the total sample size would be 280 subjects.

10.6.1 PVR

The estimates of treatment effect in PVR are obtained from three selexipag studies conducted in PAH (NS-304/-02 and TRITON [ongoing]) and CTEPH (AC-065B201) subjects, as well as in three other studies with different therapies in CTEPH [Table 8]. The NS-304/-02 study (N = 35 in PPS) confirmed a statistically significant treatment effect of selexipag versus placebo (30.3% geometric mean decrease, 95% CL: −44.7%, −12.2%; p = 0.0045) in PVR at Week 17 as primary endpoint. The AC-065B201 study (N = 28, PPS) showed a non-statistically significant 16.3% (95% CL: −34.7, +7.3) decrease from baseline in PVR in the selexipag group relative to placebo at Week 17. The IA of the ongoing study TRITON (AC-065A308) in PAH reveals an estimated coefficient of variation (CV) of 50% (blinded pooled estimate), which is larger than the values reported in other studies.

Table 8 Estimates of treatment effect in PVR

	AC-065B201	AC-065B201 subset*	NS-304/-02	TRITON
Indication	CTEPH	CTEPH	PAH	PAH
PH-background therapy	ERA, PDE5i	ERA, PDE5i	ERA, PDE5i	ERA (macitentan) + PDE5i (tadalafil)
Investigational drug	Selexipag	Selexipag	Selexipag	Selexipag
Assessment time	17 weeks	17 weeks	17 weeks	26 weeks
N (active: placebo)	PPS Active: 21 Placebo: 7	Active: 11	PPS Active: 29 Placebo: 6	238 (1:1) Enrollment ongoing
CV	Active: 29.3% Placebo: 24.3%			50% (interim pooled estimate in 79 patients)
Change from baseline ± SD (dyn.sec/cm^5)	Active: −104 ± 191 Placebo: +26 ± 180	Active: −140	Active: −168 ± 241.6 Placebo: +137.2 ± 84.9	
% change from baseline	Active: −13.4% Placebo: +2.1%		Active: −19.3% Placebo: +15.9%	
Placebo-adjusted effect from baseline & 95% CL	Ratio: −16.3% (−34.7%, 7.3%)	Not applicable	Ratio: −30.3% (−44.7%, −12.2%)	

	CHEST-1	MERIT-1	BENEFIT
Indication	CTEPH	CTEPH	CTEPH
PH-background therapy	None	PDE5i, oral/inh. Prostanoids	None
Investigational drug	Riociguat	Macitentan	Bosentan
Assessment time	16 weeks	16 weeks	16 weeks
N (active: placebo)	261 (2:1)	80 (1:1)	157 (1:1)
CV		39.4% (mean)	Active: 38.4% Placebo: 31.1%
Change from baseline ± SD (dyn.sec/cm^5)	Active: −226 ± 248 Placebo: 23 ± 274	Active: −206 ± 450.4 Placebo: −85.8 ± 301.5	
% change from baseline	Active: −28.6% Placebo: +3%		Active: -22.5% Placebo: +2.2%
Placebo-adjusted effect (difference) & 95% CL from baseline	Ratio: −31.5% (approx.) Difference (dyn.sec/cm^5): −246 (−303, −190)	Ratio: −16% (−30%, −1%)	Ratio: −24.1% (−31.5%, −16.0%)

CL = confidence limits; CTEPH = Chronic thromboembolic pulmonary hypertension; CV = coefficient of variation; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase 5 inhibitor; PH = pulmonary hypertension; PPS = Per-protocol Analysis Set; SD = standard deviation.
* Subjects with ≥3 prostacyclin-associated adverse events in the selexipag group.

Although the main analysis of PVR at Week 20 will be conducted using an ANCOVA model, calculations of sample sizes were approximated by t-test for superiority on the log-transformed PVR percent of baseline value at Week 20 using the software package EAST™ version 6.4.0.1 for ratio of means. A sample size of 90 subjects in the HES will provide a power of >90% for the treatment effect of a 30% relative improvement in geometric mean as compared to placebo with a CV of 35–50% and a two-sided significance level of 5% [Table 9].

Table 9 Sample sizes for PVR under different scenarios with two-sided 5% type I error rate and 90% power using t-test for ratio of means

Relative improvement over placebo in geomean	CV			
	35%	40%	45%	50%
20%	100	128	158	191
25%	61	78	96	116
30%	41	52	63	76
35%	29	36	44	53

CV = coefficient of variation.

10.6.2 6MWD

The estimates of treatment effect in 6MWD change from baseline in four CTEPH studies are summarized in Table 10.

Table 10 Estimates of treatment effect in 6MWD

	CHEST-1 (Riociguat)	MERIT -1 (Macitentan)	AC-065B201 (Selexipag)	AC-065B201 subset* (Selexipag)	BENEFIT (Bosentan)
Assessment time	16 weeks	24 weeks	17 weeks	17 weeks	16 weeks
Change from baseline: Active (mean ± SD)	39 ± 79	35 ± 52	19 ± 55	24.7	2.9 (95% CL: −12.9, 18.8)
Change from baseline: Placebo (mean ± SD)	−6 ± 84	1 ± 83	27 ± 49	NA	0.8 (95% CL: −18.1, 19.7)
placebo-adjusted change from baseline (mean, 95% CL)	46 (25, 67)	34 (3, 65)	−9 (−57, 39)	NA	2.2 (−22.5, 26.8)

6MWD = 6-minute walk distance; CL = confidence limits; SD = standard deviation.
* Subjects with ≥3 prostacyclin-associated adverse events in the selexipag group.

Although the main analysis of 6MWD at Week 26 will be conducted using an ANCOVA model, calculations of power were approximated by t-test for superiority on the change in 6MWD from baseline value at Week 26 using the software package EAST™ version 6.5 for difference of means.

To have an adequate power for TTCW, the sample size is determined by the need for TTCW (see below). With a sample size of 280 subjects and using the HSD error spending function with parameter $\gamma=-4$ [Hwang 1990] for one interim analysis of 6MWD at information fraction 160/280, the power will be 90% for the treatment effect of 34 m with a standard deviation of 80 m at two-sided alpha level 2.5%.

10.6.3 Time to clinical worsening (according to the CHMP definition)

This type of endpoint was evaluated in PAH subjects in the GRIPHON study [D-13.361], with a selexipag versus placebo hazard ratio of 0.73 (99% CL 0.60 – 0.91) for TTCW according to CHMP definition and a hazard ratio of 0.60 (99% CL 0.46–0.78) for specific morbidity and mortality events.

For this study, the assumptions for sample size of TTCW are a hazard ratio of 0.60, a no-event rate of 0.70 at 12 months in the placebo arm, a two-sided type I error of 2.5% and a power of 80%. Using the software package EAST™ version 6.5 for log-rank test, this setting requires a total of 148 events with two interim analyses using the OF-type error spending function [Lan 1983]. With piecewise uniform accrual rates of 3.313 subjects/month in the first 16 months and 9.125 subjects/month in the remaining time, the sample size of 280 subjects will be reached in about 41 months. The required number of events is expected to be observed 17 months after the randomization of the last subject. The estimated duration from the first subject randomized to the time when 148 events are observed plus the time to the EDBT visit is about 59 months. The actual duration depends on the actual accrual rate, the actual clinical worsening event rate, recommendation of the IDMC at interim analyses [see Section 10.4, Figure 5 and IDMC Charter Section 8 and Appendix 6] and regular safety monitoring meetings, and sponsor's decision [Section 8.3].

10.6.4 Design operating characteristics

The set-up and results of simulations to evaluate design operating characteristics under the null and alternative hypotheses are presented in the IDMC charter.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timely entry 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 (ref. to US 21 CFR Part 11).

Entries recorded by the subject in the PROs (PAH-SYMPACT®, EQ-5D-5L, WPAI©: GH) [electronic format], submitted to the central image processing center and recorded via the actigraphy device are considered source data.

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

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

11.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (eg, documents attached to SAE forms / Pregnancy Notification form) submitted to the sponsor and any CROs, subjects must be identified only by number and never by their name or initials, date of birth, hospital numbers or any other identifier. Subject identifiers might be submitted to the central image processing center. In that case, the central image processing center is contracted by the sponsor to anonymize data before submission to ACs [see Section 4.1.1]. The investigator/delegate must keep a subject identification code list at the site, showing the screening/randomization number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (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

The investigators and site personnel will have access to the site eCRF data until the database is closed. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate may be instantly alerted to data queries by validated programmed checks. Additional data review (including medical review) will be performed by sponsor personnel on an ongoing basis to look for discrepancies and unexpected patterns in data and to monitor the study. If discrepant data are detected or clarification is required, a query specifying the problem or question will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require 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 subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples will be processed through the 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 to the sponsor electronically.

Data collected by the vendors of the ePRO and actigraphy device, the imaging vendor and the IRT vendor are owned by Actelion Pharmaceuticals Ltd. The data will be sent to the sponsor electronically.

AEs and procedures are coded according to the latest 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 sponsor's appropriate QS documents. After database closure, the investigator will receive the eCRFs of the subjects of his/her site (including all data changes made) on electronic media.

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 subject (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 their legally designated representative. The investigator/delegate must explain to subjects 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 subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject and/or their legally designated representative to consider his/her decision to participate in the study, and it shall be verified that the subject has understood the information (eg, by asking the subject to explain what is going to happen).

Two study-specific ICFs will be provided: one for the hemodynamic cohort (approximately the first 90 randomized subjects) and one for the non-hemodynamic cohort. The ICFs will be provided in the country local language(s).

Site personnel (according to local regulations) authorized to participate in the consent process and/or to obtain consent from the subject and/or their 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 subject 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 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 subject and/or their legally designated representative; the original is filed in the site documentation. The informed consent process must be fully documented in the subject's medical records. This must include at a minimum the study reference, the subject number, the date and, if applicable, time when the subject was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional person present during the consent process (eg, subject's family member[s]), and the

information that a copy of the signed ICF was given to the subject / their legally designated representative.

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

Subjects who are rescreened are required to sign a new ICF. By signing the ICF, the subject or legally designated representative is authorizing the collection of information about his or her survival status [see Section 7.2.3.9].

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 subject in the event of study-related injuries will comply with applicable regulations.

Study subjects will be reimbursed for the study-related expenses (eg, travel costs, meals, hotel) and may be offered financial compensation for their participation in the study only 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 subject.

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 important protocol deviations will be reported in the CSR. IECs/IRBs will be provided with listings of protocol deviations as 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

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

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

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

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the 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 printouts must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies with the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the 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 subjects, but at least for some of them (eg, first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects), as 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. Essential documents must be provided to the sponsor before shipment of study treatment to the study site.

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 subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the SM will remotely 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. The sponsor's 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 subject recruitment rate and critical data collection times.

The PI must ensure that the eCRF is completed after a subject's visit (site visit or telephone call), and that all requested subject files (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 subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

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

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

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

being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

12.11 Inspections

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

Health authorities and/or IECs/IRBs 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 inspector(s) and allow access to all study documentation (eg, subject records) and study facilities.

12.12 Reporting of study results and publication

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

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

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

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

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

Registration of clinical studies and disclosure of results

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

13 REFERENCES

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14 APPENDICES

14.1 Appendix 1 Actelion heart catheterization guidance

For the subjects in the hemodynamic cohort hemodynamic evaluations are to be carried out according to this guidance for those conditions and hemodynamic parameters that are described below. Further hemodynamic evaluations will be carried out according to the catheterization laboratory's local practice.

14.1.1 Heart Catheterization procedures

14.1.1.1 Conditions

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

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

Where historical RHC/LHC is used for baseline measurements, then this guidance requirements for zeroing [Section 14.1.1.2] and heart catheterization measurement [Section 14.1.2] must have been followed and documented in the source notes. Otherwise a new RHC/LHC assessment will have to be performed for baseline measurements.

14.1.1.2 'Zeroing'

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

This must be documented in the heart catherization worksheet.

14.1.1.3 Oxygen

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

14.1.2 Heart catheterization measurements

14.1.2.1 Right Heart Catheterization measurements

14.1.2.1.1 Pulmonary Artery pressure (PAP)

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

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

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

14.1.2.1.2 Pulmonary artery wedge pressure (PAWP)

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

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

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

14.1.2.1.3 Cardiac Output

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

If **thermodilution method** is used:

- The CO must be measured with at least three measurements documented in the heart catherization worksheet.

- The three measurements must be within 10% of each other, ie, the lowest of the 3 CO values must not be lower than 10% of the middle value AND the highest value must not be higher than 10% of the middle value.

- If the three values are not within 10% of each other (as per above), additional measurements can be performed until 3 measurements are obtained that are within 10% of each other.

- If more than three measurements are taken, the largest and/or smallest outlying values in the opinion of the operator should be discarded until at least three values are within 10% of each other.

- If more than three values are recorded, all values must be documented in the heart catherization worksheet.

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

- Only one value is required and must be documented in the heart catherization worksheet.

- If multiple values are performed, all CO values must be documented in the heart catherization worksheet. In addition, the operator must identify the most representative and reliable CO value.

14.1.2.2 Left Heart Catheterization measurement

14.1.2.2.1 Left ventricular end diastolic pressure (LVEDP)

Left ventricular end diastolic pressure (LVEDP) is to be recorded only when PAWP is not available or not reliable.

The participant will be asked to breath normally during the procedure. The operator will assess the appropriate LVEDP reading based on the respiratory cycle and the pressure tracing.

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

The operator must identify the most representative and reliable LVEDP value on the heart catherization worksheet.

14.1.2.3 Other measurements

mRAP, dSAP, sSAP and SVO_2 are measured as per local practice.

Cardiac index (CI) and total peripheral resistance (TPR) are to be calculated as per local practice.

14.1.3 Documentation

14.1.3.1 Tracings

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

14.1.3.2 Heart catheterization worksheet

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

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

14.2 Appendix 2 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; Erythrocyte Volume fraction (EVF); Packed Cell Volume (PCV) *(male)*	< 0.32 L/L	< 0.20 L/L	> 0.60 L/L	> 0.65 L/L
Hematocrit; Erythrocyte Volume fraction; Packed Cell Volume *(female)*	< 0.28 L/L	< 0.20 L/L	> 0.55 L/L	> 0.65 L/L
Platelets *(assuming no platelet cluster)*	$< 75 \times 10^9$/L	$< 50 \times 10^9$/L	$> 600 \times 10^9$/L	$> 999 \times 10^9$/L
Leukocytes; White Blood Cells	$< 3.0 \times 10^9$/L	$< 2.0 \times 10^9$/L	$> 20.0 \times 10^9$/L	$> 100.0 \times 10^9$/L
Neutrophils (Abs)	$< 1.5 \times 10^9$/L	$< 1.0 \times 10^9$/L	NA	NA
Eosinophils (Abs)	NA	NA	$> 5.0 \times 10^9$/L	NA
Lymphocytes (Abs)	$< 0.8 \times 10^9$/L	$< 0.5 \times 10^9$/L	$> 4.0 \times 10^9$/L	$> 20 \times 10^9$/L

Grayed fields represent alert criteria for expedited notification to respective investigational site.

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
Glomerular Filtration Rate	< 60 ml/min/ 1.73 m^2	< 30 ml/min/ 1.73 m^2	NA	NA

* Additional threshold are to be reported namely > 8 × ULN.
Grayed fields represent alert criteria for expedited notification to respective investigational site.

Serum pregnancy test

A positive serum pregnancy test will also trigger an expedited notification to respective investigational site.

14.3 Appendix 3 Actelion 6MWT guidance

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

These criteria are, in part, derived from the recommendations included in the ATS Guidelines issued in 2002 and the ERS/ ATS Technical Standard published in 2014 [ATS Guidelines 2002, Holland 2014]. As opposed to the comprehensive published manuscripts, this guidance has been shortened and accustomed for use in a clinical study in which a variety of different assessments may need to be performed at a given visit. In addition, dyspnea will be assessed using the BDI scale [Appendix 4] / Borg CR10 Scale® [Borg 1998] [Appendix 5].

14.3.1 Instructions

14.3.1.1 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 20 meters in length. The track must be marked at regular intervals to facilitate measurement of the distance walked (markings every 3 meters are recommended). The turnaround points must be marked with a cone. A starting line, which marks the beginning and the end of each lap (one lap is twice the length of the track used at the site), needs to be marked on the floor.

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

The person administering the 6MWT (tester) needs to stand near the starting line during the 6MWT and must not walk with the participant, and not get distracted during the conduct of this 6MWT (eg, by talking to someone).

Rest periods are allowed if the participant can no longer continue. If the participant needs to rest, he/she may pause, lean against the wall and continue walking whenever he/she feels able. The timer must continue to run even if the participant stops to rest. The 6MWT can be stopped at any moment as due to medical emergencies or safety issues such as chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

The 6MWT is a non-encouraged test. An even tone of voice must be used when using the standard phrases. No other instructions or words of encouragement are given during the test, other than the pre-scripted phrases (see Section 14.3.3.1). 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 +/- 2 hours of the baseline test) to minimize variability.

If a participant is oxygen dependent, the use of a portable device is allowed. The oxygen flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT. Additionally, the way oxygen is delivered (delivery device, application route, way of carrying the delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.

14.3.1.2 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.

14.3.1.3 Timing

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

14.3.2 Test requirements

14.3.2.1 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 15 minutes before the test starts.
- If the participant is used to take bronchodilators, he/she must take them at least 10 to 30 min before the test.
- Walking aids (eg, cane) and walkers are not allowed.

14.3.2.2 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
- BDI scale [Appendix 4]/Borg category-ratio (CR) 10 Scale® [Appendix 5]

14.3.3 Performing the 6MWT

14.3.3.1 Instructions to the participant during the 6MWT

The tester uses the following exact dialogue with the participant:

> *"The objective of this test is to walk as far as possible in 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.*
>
> *You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation".*

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

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

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

> *"Start now, or whenever you are ready"*

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

> After the first minute: *"You are doing well. You have 5 minutes to go".*
>
> When the timer shows 4 minutes remaining: *"Keep up the good work. You have 4 minutes to go."*
>
> When the timer shows 3 minutes remaining: *"You are doing well. You are halfway done."*

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

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

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

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

The tester will not stop the timer. If the participant stops before the 6 minutes are up and refuses to continue (or the tester decides that they should not continue), the tester wheels the chair over for the 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!"

14.3.3.2 Assessments after the 6MWT

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

The tester shows the BDI scale [Appendix 4]/Borg category-ratio (CR) 10 Scale® [Appendix 5] to the participant and asks the participant:

"Please grade your dyspnea using this scale".

14.3.4 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.

14.4 Appendix 4 Borg dyspnea index (BDI) scale

As soon as possible following the walk test, the subject is asked to rate his/her dyspnea using the following BDI scale. The tester will use the following dialogue:

"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)

14.5 Appendix 5 Borg CR10 scale®

14.5.1 Instructions

The Borg CR10 Scale® will be explained in detail to the participants at Screening before starting the first 6MWT (questionnaires and instructions will be provided in local language).

The tester will provide the following instruction to the participant:

"Use this rating scale to report how strong your perception of dyspnea. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or "Extremely strong", "Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". If your feeling is "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", - "Extremely strong", "Maximal"–you can use a larger number, eg 12 or still higher (that's why "Absolute maximum" is marked with a dot "•").

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating dyspnea give a number that corresponds to how hard and strenuous you perceive your breathing to be[7]. The perception of dyspnea is mainly the feeling that one cannot breathe well enough.

0 - "Nothing at all", means that you don't feel any shortness of breath.

1 - "Very weak" means a very light shortness of breath.

3 - "Moderate" is somewhat but not especially hard. You are somewhat shorter of breath.

5 - "Strong". Breathing is getting difficult. The effort to breathe is about half as intense as "Maximal".

[7] 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.

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.

Any questions?”

14.5.2 Borg CR10 Scale®

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

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

14.6 Appendix 6 WHO function classification of Pulmonary Hypertension

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

14.7 Appendix 7 PAH-SYMPACT® questionnaire

The questionnaire and a patient manual will be available in the local language(s).

DAY 1

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.

DAYS 2-6 (Subsequent days prior to last day in week)

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS**. Please select the answer that best describes your experience with your **symptoms.**

Please do not skip any questions. There are no right or wrong answers to any of the questions.

DAY 7 (Last day of week)

INSTRUCTIONS

Today you will answer questions about your Pulmonary Arterial Hypertension symptoms over the **PAST 24 HOURS** and additional questions about how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS**.

Please do not skip any questions. There are no right or wrong answers to any of the questions.

SYMPTOMS

1. In the past 24 hours …

Did you use oxygen?
☐0 No
☐1 Yes If yes: How many hours? _____

Answer the questions that follow based on your experiences **regardless of whether you were using oxygen or not.**

2. In the past 24 hours …

How would you rate your **shortness of breath**?
☐0 No shortness of breath at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

3. In the past 24 hours …

How would you rate your **fatigue**?
☐0 No fatigue at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

4. In the past 24 hours …

How would you rate your **lack of energy**?
☐0 No lack of energy at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

5. In the past 24 hours …

How would you rate the **swelling in your ankles or legs**?
☐0 No swelling in ankles or legs at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

6. In the past 24 hours …

How would you rate the **swelling in your stomach area**?
☐0 No swelling in stomach area at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

7. In the past 24 hours …

How would you rate your **cough**?
☐0 No cough at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

8. In the past 24 hours …

How would you rate your **heart palpitations (heart fluttering)**?
☐0 No heart palpitations (heart fluttering) at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

9. In the past 24 hours …

How would you rate your **rapid heartbeat**?
☐0 No rapid heartbeat at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

10. In the past 24 hours …

How would you rate your **chest pain**?
☐0 No chest pain at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

11. In the past 24 hours …

How would you rate your **chest tightness**?
☐0 No chest tightness at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

12. In the past 24 hours …

How would you rate your **lightheadedness**?
☐0 No lightheadedness at all
☐1 Mild
☐2 Moderate
☐3 Severe
☐4 Very Severe

IMPACTS

For the following questions, please select the answer that best describes how your life was affected by Pulmonary Arterial Hypertension in the **PAST 7 DAYS.** Answer the questions based on your experiences regardless of whether you were using oxygen or not.

1. In the past 7 days …

   Were you able to **walk slowly on a flat surface**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

2. In the past 7 days …

   Were you able to **walk quickly on a flat surface**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

3. In the past 7 days …

   Were you able to **walk up hill**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

4. In the past 7 days …

   Were you able to **carry things**, such as bags or baskets?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

5. In the past 7 days …

   Were you able to **do light indoor household chores**, such as preparing food, cleaning surfaces, or tidying up?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

6. In the past 7 days …

   Were you able to **wash or dress yourself**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

7. In the past 7 days …

   How much did you **need help from others**?
   ☐0 Not at all
   ☐1 A little bit
   ☐2 Some
   ☐3 Quite a bit
   ☐4 Very much

8. In the past 7 days …

   Were you able to **think clearly**?
   ☐0 Yes, with no difficulty at all
   ☐1 Yes, with a little difficulty
   ☐2 Yes, with some difficulty
   ☐3 Yes, with much difficulty
   ☐4 No, not able at all

9. In the past 7 days …

   How **sad** did you feel?
   ☐0 Not at all
   ☐1 A little bit
   ☐2 Somewhat
   ☐3 Very
   ☐4 Extremely

10. In the past 7 days …

    How **worried** did you feel?
    ☐0 Not at all
    ☐1 A little bit
    ☐2 Somewhat
    ☐3 Very
    ☐4 Extremely

11. In the past 7 days …

    How **frustrated** did you feel?
    ☐0 Not at all
    ☐1 A little bit
    ☐2 Somewhat
    ☐3 Very
    ☐4 Extremely

14.8 Appendix 8 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

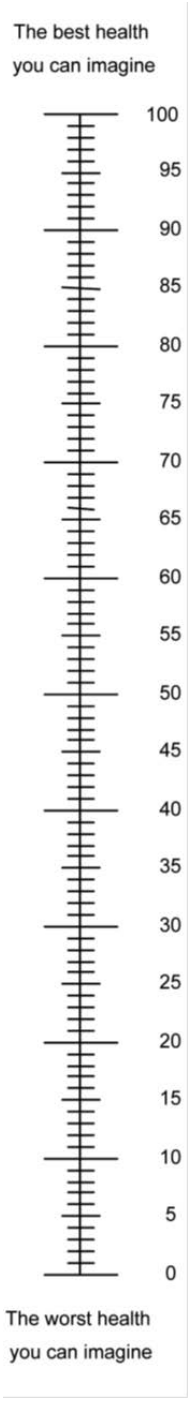
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

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 = ☐



14.9 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 seven days**, not including today.

2. During the past seven days, how many hours did you miss from work <u>because of your health problems</u>? Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS (If "0", skip to question 6.)

5. During the past seven days, how much did your health problems affect your productivity while you were working?
   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

   Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?
   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

   Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

   CIRCLE A NUMBER

14.10 Appendix 10 Child-Pugh classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to the following table [FDA 2003]:

Table 11 Child-Pugh Classification

	Score		
	1	**2**	**3**
Total bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy*	Grade 0	Grade 1-2	Grade 3-4
Prothrombin time (seconds prolonged)	<4	4-6	>6
or			
INR [Child-Pugh 2012]	<1.7	1.7 – 2.2	>2.2

INR = International normalized ratio

*Hepatic encephalopathy scoring will be based on the following criteria:
• Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram.
• Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, five cycles per second waves.
• Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
• Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
• Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cycles per second delta activity.

- Class A: Score 5-6
- Class B: Score 7-9
- Class C: Score 10-15

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 (TOC) and the previous two amendments have been included in this appendix.

Amendment 2 [(16 April 2020)]

Overall Rationale for the Amendment:

Time to clinical worsening (TTCW) has been identified as an important clinical endpoint in addition to improvement in exercise capacity (6-minute walk distance [6MWD]) [Divers 2017], and has been accepted by health authorities as an endpoint. Therefore, a study powered for TTCW would provide additional clinical data to support clinical treatment decisions in chronic thromboembolic pulmonary hypertension (CTEPH). The sponsor has revised the study design to power the study for the additional clinical endpoint, TTCW. Consequently, elements of the study design, key secondary endpoints, sample size, testing hierarchy and analysis timepoints have been amended to ensure the evaluation of 6MWD and TTCW endpoints. These design changes will be used for efficacy confirmation based on 6MWD and TTCW endpoints.

In addition, this amendment implements the sponsor's standardized guidelines for the assessment of heart catheterization (HC), 6-minute walk test (6MWT) and Borg dyspnea index (BDI), and addition of the Borg category-ratio 10 (Borg CR10) Scale® and a Clinical Event Committee (CEC) to the study.

Section Number and Name	Description of Change	Brief Rationale
Title Page PROTOCOL SYNOPSIS AC-065B302; 3.1. Study Design; 3.2. Study Design Rationale; 3.4.2. Independent Data Monitoring Committee; 5.1.5. Blinding; 5.1.10. Premature Discontinuation of Study Treatment; 7. Visit Schedule and Study Assessments; 8.1. Study Completion as per Protocol;	Changes made to study periods and visit schedule.	To power the study for the TTCW endpoint, the duration of observation of subjects on double-blind (DB) treatment was prolonged. The open-label period was shortened to the time required until the DB period results become available.

Section Number and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS AC-065B302; 3.1.1.2 Treatment period Figure 1 Study design; 3.1.2 Study duration Table 4 Open-label treatment period: visit and assessment schedule	Changes made to the OL treatment extension period and visit schedule.	On-site visits every 26 weeks were added for subjects who were transitioned to the OL treatment extension period before implementation of the AC-065B302 protocol amendment 2. This is to ensure follow-up of these subjects until the availability of the double-blind period results.
PROTOCOL SYNOPSIS AC-065B302; 2.2. Secondary Objectives; 3.2.2. Rationale for the Duration of the Study; 10.3.1. Overall testing Strategy; 10.3.3. Analysis of Secondary Efficacy Variable(s); 10.4. Interim Analyses; 10.6. Sample Size; 10.6.3. Time to Clinical Worsening	Place TTCW as a key secondary endpoint with the other key secondary endpoint, 6MWD. The testing hierarchy is modified accordingly. The sample size is increased, and the DB treatment period is modified with variable follow-up.	TTCW is an important clinical endpoint, justified as a key secondary endpoint. With variable follow-up in the DB treatment period, the chance of observing clinical worsening events has increased.
10.1.4.3. TTCW Per-protocol analysis set; 10.1.7. Usage of the Analysis Sets; Table 6 Analysis sets and their usage at each analysis time point;	Added Per-protocol set for TTCW.	TTCW is a key secondary endpoint.

Section Number and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS AC-065B302; 3.1. Study Design; 5.1.5. Blinding; 5.1.6.1. Timing of Study Analyses; 10.1.7. Use of the Analyses Sets; 10.3.1. Overall testing Strategy; 10.3.3. Analysis of Secondary Efficacy Variable(s); 10.4. Interim Analyses; 10.5. Double-blind and Open-label Analyses; 10.6. Sample Size	Change in analysis time points.	As the sample size is increased and the DB treatment period is prolonged, one additional interim analysis time point is considered appropriate.
PROTOCOL SYNOPSIS AC-065B302; 4.1. Subject population description; 4.3. Inclusion criteria	The lower limit of age for inclusion in the study was clarified as being 18 or the legal age of consent in the jurisdiction in which the study is taking place.	Amended for clarity at the request of Ethics committee.
PROTOCOL SYNOPSIS AC-065B302; 4.3. Inclusion criteria	For the non-hemodynamic cohort, the pulmonary vascular resistance (PVR) threshold for inclusion will be ≥300 dyn.sec/cm5 or ≥3.75 Wood units.	The non-hemodynamic cohort will not contribute to the primary endpoint of change in PVR at Week 20. For this reason, the amended PVR is deemed more appropriate as an inclusion criterion for this cohort.
PROTOCOL SYNOPSIS AC-065B302; 3.1. Study Design; 5.1.4. Treatment Assignment; 10.3.5. Subgroup Analyses	The stratification factor of CTEPH population was redefined to inoperable (with or without balloon pulmonary angioplasty [BPA]) versus persistent/recurrent after pulmonary endarterectomy (PEA) (including PEA followed by BPA).	It is anticipated that the use of BPA as an intervention may increase over the course of the study. It would be appropriate to have both inoperable and persistent/recurrent CTEPH sub-populations balanced in the two treatment arms.

Section Number and Name	Description of Change	Brief Rationale
7.1. General Information Table 5;	Assessments for subjects entering the post-treatment observation period (PTOP) are changed.	Subjects who discontinue from DB study treatment before the end-of-double-blind period should continue with all visits and assessments up to the PTOP-End-of-Study (EOS) to comply with the intent-to-treat principle.
3.2.2. Rationale for the Duration of the Study; 3.2.3. Rationale for the Post-treatment Observation Period; 5.1.10. Premature Discontinuation of Study Treatment; 7.1. General Information 7.2.3.9. Survival Follow-up	Long-term survival information will be collected for subjects who prematurely discontinue DB study treatment and do not agree to continue to perform the visits and assessments until the PTOP-EOS visit.	Mortality analysis can be biased due to informative censoring by competing risks. To reduce such bias, long-term survival data would be relevant to collect on subjects who have prematurely discontinued the DB study treatment.
3.4.3. Adjudication Committees	Clarification that the adjudication committee's (AC) role is to confirm CTEPH diagnosis, persistence/recurrence of pulmonary hypertension (PH) (when applicable) and inoperability.	Clarification of the role of the ACs.
PROTOCOL SYNOPSIS AC-065B302; 3.4.4. Clinical Event Committee; 6.1.2. Secondary Efficacy Endpoints; 10.3.3. Analysis of Secondary Efficacy Variables	Addition of a clinical event committee (CEC).	The CEC will ensure an independent adjudication of clinical worsening events.

Section Number and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS AC-065B302; 4.1.1. Adjudication procedure; 4.3. Inclusion Criteria; 7.1. General Information; 7.2.3.1. Right Heart Catheterization (and Left Heart Catheterization, if Needed)	The time window for baseline hemodynamic data in case of rescreening was extended.	This timeframe was deemed appropriate by the Central Adjudication Committee (CAC) to maintain robust baseline hemodynamic data while avoiding repeating the HC procedure within a short time frame for subjects who are rescreened.
PROTOCOL SYNOPSIS AC-065B302; 3.1.1.4. Post-treatment Observation Period; 5.1.2. Study Treatment Administration; 5.1.3. Study Treatment Up-titration; 5.1.9. Study Treatment Dose Adjustments and Interruptions	Introduction of once daily dosing frequency for subjects with moderate hepatic impairment (Child-Pugh B).	To align with selexipag product information.
PROTOCOL SYNOPSIS AC-065B302; 4.4.3. Exclusion Criteria related to Selexipag Use; 5.1.11.2. Hepatic Impairment	Clarification provided for exclusion criterion #12.	Exclusion criterion #12 was clarified for consistency in the selexipag development program to indicate that Child-Pugh scoring is only required in patients with hepatic impairment and does not apply to patients with no hepatic impairment.
PROTOCOL SYNOPSIS AC-065B302; 4.4.3. Exclusion Criteria related to Selexipag Use; 5.1.3. Study Treatment Up-titration; 5.1.9. Study Treatment Dose Adjustments and Interruptions	Caution when administering strong inhibitors of UGT1A3 and UGT2B7 and moderate inducer of CYP2C8 added.	Included for completeness as per Ethics Committees request.
7.1. General Information;	Removal of patient experience survey.	The survey will not be conducted due to logistical challenges.

Section Number and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS AC-065B302; 6.1.2. Secondary Efficacy Endpoints; 6.1.3. Other Efficacy Endpoints; 10.2.2. Secondary Efficacy Variable(s); 10.2.3. Other Efficacy Variable(s); 10.3.3. Analysis of Secondary Efficacy Variable(s)	Specify the changes from baseline to Week 26 in the two symptoms domains of PAH-SYMPACT® as secondary endpoint and from baseline to Week 39 in all four domains as exploratory endpoint.	Analysis strategy alignment with other ongoing sponsor's selexipag studies.
PROTOCOL SYNOPSIS AC-065B302; 3.1. Study Design; 5.1.6.1. Timing of Study Analyses; 10.1.7. Use of the Analyses Sets; 10.3.1. Overall testing Strategy; 10.3.3. Analysis of Secondary Efficacy Variable(s); 10.4. Interim Analyses; 10.5. Double-blind and Open-label Analyses; 10.6. Sample Size	Changes in the decision flow throughout the conduct of the study. 6MWD endpoint was removed from the interim analysis time point 1.	The new flow takes into account new analysis time points and depends on results of PVR, 6MWD and TTCW. To allow the collection of sufficient data for TTCW and other endpoints at later time points.
PROTOCOL SYNOPSIS AC-065B302; 2.2 Secondary objectives; 3.2.2. Rationale for the Duration of the Study; 6.1.2. Secondary Efficacy Endpoints; 10.3.3. Analysis of Secondary Efficacy Variable(s)	Changed rate of death or hospitalizations related to PH worsening up to Week 52 to all-cause death or hospitalizations related to PH worsening, and added log-rank test as the main analysis.	The log-rank test is for time to all-cause death or hospitalizations related to PH worsening. This is clinically relevant.

Section Number and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS AC-065B302; 3.1. Study Design; 3.2.2. Rationale for the Duration of the Study; 3.3. Site Personnel and Roles; 3.4.3. Adjudication Committees; 4.1.1. Adjudication Procedure; 4.3. Inclusion Criteria; 4.4. Exclusion Criteria; 5.2.3. Auxiliary Medicinal Products; 5.2.5. Forbidden Concomitant Therapy; 7.1.1. Screening/rescreening; 7.1.2. Unscheduled Visits; 7.2.2. Assessment for Diagnosis of CTEPH and Judgment of Inoperability; 7.2.3. Efficacy Assessments; 10.3.2. Analysis of Primary Efficacy Variable(s); 14.1. Actelion Heart Catheterization Guidance	Clarifying HC in the study and update the guidelines for HC.	To implement the sponsor's standardized guidelines for the assessment of HC.
14.3. Actelion 6MWT Guidance	Actelion 6MWT guidance updated.	To implement the sponsor's standardized guidelines for the assessment of 6MWD.
14.4. Borg Dyspnea Index (BDI) Scale	Borg Dyspnea Index (BDI) scale updated.	To implement the standardized guidelines for the assessment of BDI.

Section Number and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS AC-065B302; 7.2.3.3. Post-6MWT dyspnea; 14.5. Borg CR10 Scale®	Borg CR10 Scale® added.	To implement the standardized guidelines for the assessment of Borg CR10® Scale.
7.1.2. Unscheduled Visits; 7.2. Study assessments	Mandatory unscheduled visits added in case of World Health Organization (WHO) functional class (FC) increase or 6MWD decrease from baseline.	Confirmation of clinical deterioration is needed for confirmation of clinical worsening.
6.1.3. Other Efficacy Endpoints; 7.2.3.5. Daily Life Physical Activity (DLPA); 10.2.3. Other Efficacy Variables	Changes in parameters of daily life physical activity (DLPA)	Based on the experience in the TRACE study and health authority interaction.
4.5.2. Acceptable Methods of Contraception	Updated acceptable methods of contraception for hormonal contraceptive initiated during the study.	To be consistent with the Janssen protocol template and to ensure that there is a constant contraception method for the enrolled subjects while in the study.
Throughout the protocol	Inconsistencies within the protocol and with Janssen processes addressed.	To be consistent with the Janssen protocol template and style guide.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (09 January 2019)

Overall Rationale for the Amendment:

The sponsor has revised several inclusion criteria with the aim of ensuring the recruitment of subjects who could potentially benefit from medical therapy (only technically non-operable subjects assessed based on imaging review for all CTEPH subpopulation) and with substantially impaired pulmonary vascular function (PVR ≥400 dyn.sec/cm^5 or ≥5 Wood units). In addition, statistical changes have been made following interactions with health authorities.

Section Number and Name	Description of Change	Brief Rationale
Synopsis 4.3. Inclusion Criteria	To change the inclusion criteria for the study population to subjects with CTEPH who are diagnosed as inoperable (ie, technically non-operable) or with persistent/recurrent pulmonary hypertension (PH). Subjects with inoperability defined as technically operable with non-acceptable surgical risk/benefit ratio will not be included in this study. In addition, the study population will be limited to subjects with pulmonary vascular resistance at rest ≥400 dyn.sec/cm^5 or ≥5 Wood units.	To ensure the recruitment of subjects with substantially impaired pulmonary vascular function.
4.3. Inclusion Criteria	Clarification of inclusion criterion #4.	To avoid any ambiguity regarding the degree of symptoms that needs to be demonstrated, the term 'symptomatic' has been removed.
10.3.1 Overall testing strategy 10.4 Interim analysis	The Pocock-type error spending function is replaced by the Hwang, Shih and DeCani's error spending function with parameter $\gamma=-4$. Remaining secondary endpoints will be tested using an O'Brien and Fleming's error spending function.	To implement a more conservative interim type I error spending strategy for 6-minute walk distance.
Table 1 4.3 Inclusion criteria 7.2.2 Assessments for diagnosis of CTEPH and judgment of inoperability	To change the data required for eligibility review by the adjudication committees (ACs). At least one post-surgery imaging and the historical surgery and intervention report will be submitted to the ACs for both post-pulmonary endarterectomy (PEA) and post-balloon pulmonary angioplasty (BPA) subjects.	To allow exclusion of subjects with persistent/recurrent PH due to proximal disease.
3.1.1.4 Post-treatment observation period Table 5	The sequence and naming of PTOP visits have been amended.	To allow collection of Week 52 data in the PTOP in case of DB study treatment discontinuation after Week 48.
Table 5	The rules for adverse events (AE)/ serious adverse event (SAE) reporting and follow-up have been clarified.	To collect all AEs and SAEs in the PTOP period.
Throughout the protocol	The description of the patient population has been clarified.	To allow designation of PEA as surgical treatment and BPA as interventional treatment.
5.1.3 Study treatment up-titration	The use of moderate cytochrome P-450 (CYP) 2C8 inhibitors (eg, clopidogrel, deferasirox, teriflunomide) is now permitted.	Following new data from a Phase 1 study (AC-065-117; Selexipag IB), the use of moderate CYP2C8 inhibitors is

Section Number and Name	Description of Change	Brief Rationale
5.1.3.1 Double-blind study treatment up-titration 5.1.9 Study treatment dose adjustments and interruptions		permitted but requires the selexipag dosing frequency to be once daily. The dose will be taken in the morning to allow post-dose efficacy assessments. Dosing frequency must be changed to twice daily when co-administration of the moderate CYP2C8 inhibitor is stopped.
5.2.5 Forbidden concomitant therapy	The timing regarding the permitted use of prostacyclin or analogs has been clarified.	To allow rescue therapy with prostacyclin or analogs immediately after study treatment interruption.
7.2.3.5 Daily life physical activity (DLPA) 7.2.6.1 PAH-SYMPACT™ questionnaire	Conditions of use of contract research organization (CROs) devices (actigraphy and hand-held mobile device for PAH-SYMPACT®) have been clarified.	To align with the selected devices for the study that require different set-up methods and offer different data upload options.
6.1.3 Other efficacy endpoints Table 3 7.2 Study assessments 7.2.3.8 Clinician reported outcomes 10.2.3 Other efficacy variables	Additional exploratory endpoints have been introduced.	This is to prospectively assess the impact of selexipag versus placebo on risk stratification, on Clinician Global Impression of Severity and Clinician Global Impression of Change.
6.1.3 Other efficacy endpoints 10.2.3 Other efficacy variables	The change from baseline in PAH-SYMPACT® scores will be assessed at Week 39 instead of Week 52 in the exploratory endpoints.	PAH-SYMPACT® scores are assessed for 7 days after the last visit; therefore, they cannot be assessed beyond Week 52, as the open-label study treatment starts in the evening of Week 52.
Appendix 8	The Hospital Anxiety and Depression Scale (HADS) questionnaire has been removed.	A license for use is not available.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Actelion Pharmaceuticals Ltd
Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

Protocol Title

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, group-sequential, adaptive, Phase 3 study with open-label extension period to assess the efficacy and safety of selexipag as an add-on to standard of care therapy in subjects with inoperable or persistent/recurrent after surgical and/or interventional treatment Chronic Thromboembolic Pulmonary Hypertension.

SELECT: SELExipag in inoperable or persistent/recurrent Chronic Thromboembolic pulmonary hypertension

Protocol AC-065B302; Phase 3

JNJ-67896049 / ACT-293987 Selexipag

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

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

EudraCT NUMBER: 2018-002823-41

Status: Approved
Date: 16 June 2020
Prepared by: Actelion Pharmaceuticals Ltd, a division of Janssen Research & Development
EDMS number: D-20.207

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

In alignment with recent health authority guidance, the sponsor is providing options for study related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at risk, study treatment will be discontinued, and study follow-up will be conducted.

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

Every effort should be made to adhere to protocol-specified assessments for subjects on study treatment, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the subject, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study treatment and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

- Related to Protocol Section 5.1.7.3 Study treatment dispensing
  - For subjects unable to visit the clinic/hospital, direct-to-patient (DTP) shipment of study drugs may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP shipments are deemed necessary, the process should be coordinated between the site and sponsor staff following the "COVID-19 DTP Guidance Document".
- Related to Protocol Section 7.2.6 Patient reported outcomes
  - The PAH-SYMPACT® questionnaire will be assessed for the seven consecutive days following the remote/virtual visit when an on-site visit is not possible.
  - The EQ-5D-5L and the WPAI©: GH scores will be collected via a remote/virtual visit and entered on an electronic device by the site staff when an on-site visit is not possible.
- Related to Protocol Section 12.3 Informed consent
  - Consenting and re-consenting of subjects will be performed as applicable for the measures taken (including remote consenting by phone or video consultation) and according to local guidance for informed consent as applicable.

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 treatment, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Actelion Pharmaceuticals Ltd, Janssen Research & Development

Signature: PPD _____ Date: PPD

(Day Month Year)

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