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

Clinical Protocol

Protocol Title

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Period to Assess the Efficacy and Safety of Selexipag as Add-On Treatment to Standard of Care in Children Aged ≥2 to <18 years with Pulmonary Arterial Hypertension

SALTO

Protocol AC-065A310; Phase 3, Version 7
Amendment 5

JNJ-67896049 / ACT-293987 (selexipag)

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

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Prepared by: Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson
EDMS number: EDMS-RIM-265811, 5.0
GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Protocol Version 7 - Global Amendment 5	1 March 2023
Protocol Version 6 - Global Amendment 4	08-Apr-2022
Guidance on Study Conduct During A Natural Disaster/Major Disruption/Pandemic (EDMS-RIM-263730, 4.0)	08-Apr-2022
Protocol Version 5 - Global Amendment 3	20-May-2021
COVID-19 Appendix (EDMS-RIM-263730, 3.0)	19-May-2021
Protocol Version 4 - Global Amendment 2	13-Oct-2020
COVID-19 Appendix (EDMS-RIM-263730, 2.0)	03-Aug-2020
Protocol Version 3 - Global Amendment 1	06-Mar-2020
Protocol Version 2*	29-Aug-2019
Version 1	24-Jul-2019

*first globally submitted protocol version

Amendment 5 (1 March 2023)

Overall Rationale for the Amendment:

The main reason for the current amendment is to mitigate the lower than anticipated recruitment rate in SALTO. The main changes are:

1. To modify the analysis of the primary endpoint from a powered event-driven approach to a descriptive analysis with otherwise unchanged study conduct and data collection (including blinding, randomization, and the placebo-controlled study design).
2. To modify the maximum sample size from 237 to approximately 125 participants.
3. To upgrade the change from baseline to Week 24 of NT-proBNP from an exploratory endpoint to a secondary endpoint.

Other changes are consequential updates to applicable sections, clarifications, and changes due to an update of the protocol template. The changes made to clinical protocol AC-065A310 as part of Protocol Amendment 5 are listed below, including the rationale for each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.7 Appendix 7: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Title page; 1.1: Synopsis, Objectives and Endpoints; 1.1: Synopsis, Overall Design; 1.1: Synopsis, Number of Participants; 1.1: Synopsis, Intervention Groups and Duration; 1.1: Synopsis, Statistical Methods, Sample Size Determination; 1.2: Schema, Figure 1; 3: Objectives and Endpoints; 4.1: Overall Design; 4.2: Scientific Rationale for Study Design; 9.1: Statistical Hypotheses; 9.2: Analysis Timepoints; 9.4: Populations for Analyses; 9.5: Statistical Analyses; 9.5.1: Primary Efficacy Analysis; 9.5.2: Secondary Efficacy Analysis; 9.5.2.2: Time to First CEC-confirmed Hospitalization for PAH or Death Due to PAH; 9.7: Interim Analysis	The analysis of the primary endpoint was changed from a powered event-driven approach (when required number of primary endpoint events has been reached) to a descriptive analysis. Three analysis timepoints are planned within the double-blind treatment period (Analysis 1, Analysis 2 and Analysis 3). Otherwise, there is no change to the study conduct, data collection, blinding, randomization, and the placebo-controlled design. The terms “event-driven” and “group sequential” were consequently deleted throughout the protocol. Figure 1 was updated to align with changes in analyses. Section 9.5.2.2: Time to First CEC-confirmed Hospitalization for PAH or Death Due to PAH was added.	Analyses were updated as per the main changes in the current amendment listed above the table, ie, (1) and (2). In addition, the primary efficacy analysis was revised in alignment with the other protocol changes.
1.1: Synopsis, Overall Design; 4.1: Overall Design	The following was deleted: Two important milestones for two specific Health Authorities (ie, by CCI [redacted]) will trigger the analysis timepoints regardless on the observed number of events.	Analyses were updated as per the main changes in the current amendment listed above the table, ie, (1) and (2).
1.1: Synopsis, Overall Design; 1.1: Synopsis, Number of Participants; 1.1: Synopsis, Intervention Groups and Duration; 1.1: Synopsis, Statistical Methods, Sample Size Determination; 9.2: Analysis Timepoints; 9.3: Sample Size Determination	The total number of participants expected to be randomized was changed from 237 to approximately 125.	Analyses were updated as per the main changes in the current amendment listed above the table, ie, (1) and (2).
2.3: Benefit/Risk Assessment; 4.1: Overall Design	“Primary analysis” was replaced with “Analysis 2”.	The Analysis 2 results are the basis for the benefit-risk assessment and start of the OLEP, not the primary analysis.

Section Number and Name	Description of Change	Brief Rationale
4.1: Overall Design; 4.2: Scientific Rationale for Study Design; 6.3: Measures to Minimize Bias: Randomization and Blinding; 9: Statistical Considerations; 9.2: Analysis Timepoints	It was clarified that the blinded study team will remain blinded until database lock for Analysis 2. An independent submission team will be unblinded to data and perform Analysis 1 in order to prepare for interactions with health authorities. Details will be documented in a separate charter, which will be finalized prior to Analysis 1.	Clarification on maintaining data integrity between Analysis 1 and Analysis 2.
1.1: Synopsis, Overall Design; 4.1: Overall Design	The following was deleted: Analysis 1 and 2 may be combined in case less than 60 CEC-confirmed primary endpoint events have been observed by CCI [redacted]. The study will then continue in a double-blind fashion until Analysis 3. These analyses are performed following two different analysis strategies up to PPD (PPD and up to PPD in consideration of different requirements from Health Authorities.	Analyses were updated as per the main changes in the current amendment listed above the table, ie, (1) and (2).
4.1: Overall Design	Figure 2: Global Study design and submission/analyses strategies was deleted.	Analyses were updated as per the main changes in the current amendment listed above the table, ie, (1) and (2).
4.1: Overall Design	A following clarification was made: The duration of the double-blind treatment period will be different for ~~each~~ individual participant**s** and will depend on the time of entering the study **and will last until all participants included in Analysis 2 have completed their EOT visit**. ~~Participants will continue double-blind study intervention up to October 2024 at the latest.~~ Participants may discontinue double-blind treatment early (eg, due to an AE or initiation of parenteral or inhaled prostacyclin treatment).	Analyses were updated as per the main changes in the current amendment listed above the table, ie, (1) and (2).

Section Number and Name	Description of Change	Brief Rationale
1.1: Synopsis, Objectives and Endpoints; 1.3.1: Visit and Assessment Schedule During Double-blind Treatment Period Uptitration Period Until Week 12; 1.3.2: Visits and Assessments After Week 12 - for Participants Continuing Double-blind Study Drug Treatment until End of Study; 1.3.3: Visits and Assessments after EOT - for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study; 3: Objectives and Endpoints; 9.2: Analysis Timepoints; 9.3: Sample Size Determination; 9.5: Statistical Analyses; 9.5.2: Secondary Efficacy Analysis; 9.5.2.1: NT-proBNP	The following change was made in secondary endpoints: – NT-proBNP change from baseline to Week 24 was promoted to a secondary endpoint. Details for NT-proBNP change from baseline to Week 24 (ie, $\log_2$(Week 24/Baseline)) were added as it was promoted to a secondary endpoint. NT-proBNP responder at Week 24 will be a supplementary estimand. Serum NT-proBNP was deleted from Clinical Laboratory Tests and added to Efficacy Assessments in Section 1.3.1, Section 1.3.2, and Section 1.3.3. Section 9.5.2.1: NT-proBNP was added.	NT-proBNP change from baseline to Week 24 was upgraded from an exploratory endpoint to a secondary endpoint.
4.2: Scientific Rationale for Study Design	Background on NT-proBNP as a biomarker was included.	NT-proBNP change from baseline to Week 24 was upgraded from an exploratory endpoint to a secondary endpoint.
9.6: Other Analyses	Other exploratory endpoints, as well as the OLEP endpoints, will be summarized with descriptive statistics by intervention group. ~~Comparisons between intervention groups~~ **Details** will be specified in ~~the~~ SAP**s**.	Formal comparisons between treatment groups are not applicable for exploratory endpoints.
1.3.4: Visits and Assessments During the Open-Label Extension Period, footnote *ee*; 4.1: Overall Design; 6.8: Intervention After the End of the Study	Participants who will benefit from study treatment during the OLEP will be able to receive continued access to study treatment via the following options: by switching to commercial Uptravi, to PTA program or to an open-label study for long-term follow-up. Details for transitioning to continued access for participants who complete OLEP and benefit from study treatment were added.	Participants who benefit from study treatment during the OLEP may be able to receive continued access to the study treatment at the end of their participation in the OLEP. Additional details were added to clarify transitioning to continued access options.
1.3.1: Visit and Assessment Schedule During Double-blind Treatment Period Uptitration Period Until Week 12, footnote *l*	TSH will be assessed at each time point**, except Visit 1 (screening)**; thyroid antibodies will be assessed at Visit 2 and thereafter only when medically indicated; Free T3 and free T4 will be assessed in case TSH is abnormal or when medically indicated.	A clarification was made that TSH will be assessed at each time point, except Visit 1 (screening).

Section Number and Name	Description of Change	Brief Rationale
1.3.3: Visits and Assessments after EOT – for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study, footnote *bb*; 10.16.12: Safety Assessments	Hematology tests must be assessed monthly during the first 4 months of treatment with study treatment bosentan and quarterly thereafter, and not monthly during the first 6 months as per Tracleer EU SmPC.	The changes were made to clarify ambiguous instruction on regular hemoglobin testing in participants receiving study treatment bosentan after disease progression (ie, PCC dated 12 May 2022 was integrated).
1.1: Synopsis, Objectives and Endpoints; 3: Objectives and Endpoints	Time to ~~disease progression~~ **clinical worsening** from randomization up to 7 days after study treatment discontinuation, ~~with disease progression~~ **where clinical worsening is** defined as **at least one of the following components (adapted from the CHMP definition [EMEA 2008])**: (…) iii. **new or worsening** signs or symptoms of right-side~~d~~ heart failure.	Wording for the exploratory endpoint time to disease progression was changed to differentiate it from the primary endpoint.
1.1: Synopsis, Pharmacokinetic Evaluations; 8.7: Pharmacokinetics	~~Plasma collected for pharmacokinetics (PK) may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.~~	The change was made to clarify the use of leftover plasma from pharmacokinetic samples, ie, any left-over from pharmacokinetic trough sampling will not be used for any additional analyses.
10.4: Appendix 4: Regulatory, Ethical, and Study Oversight Considerations, Committees Structure	The following changes were made: A CEC consisting of independent PAH experts including pediatricians will be appointed to ~~review and~~ adjudicate primary endpoint events of the study in a blinded fashion (refer to Section 8.2.1.3). Committee membership, responsibilities, authorities, and procedures ~~will be~~**are** documented in its charter. **In the presence of disease progression (elements of the primary endpoint as defined in Section 3), a patient dossier will be compiled and provided to the CEC for review.** ~~For exhaustive and systematic adjudication, participant cases will be submitted to the CEC if at least one of the following conditions is reported by the investigator:~~ ~~• Disease progression events (refer to Section 8.2.1),~~ ~~• Death,~~ ~~• (S)AEs denoting PAH worsening/right heart failure (pre-specified list of MedDRA terms in CEC Charter),~~ ~~• Interventions such as lung transplantation, atrial septostomy and Pott's anastomosis,~~ ~~• Initiation of PAH specific medication, or~~ ~~• Initiation of iv diuretics or chronic use of oxygen.~~	The changes were made to align with the current CEC process and Charter, ie, disease progression events are reported and submitted to the CEC by the study investigators.

Section Number and Name	Description of Change	Brief Rationale
10.11: Appendix 11: Child-Pugh Classification	The following changes were made to Table 6, Child-Pugh Classification: – The thresholds for total bilirubin were changed from decimal numbers to whole numbers. – Serum albumin levels for classification 2 were changed from 25-35 g/L to 28-35 g/L.	The conversion of total bilirubin to mmol/L resulted in decimal places which cannot be considered by the Central Lab system, therefore, the thresholds for total bilirubin should be provided in whole numbers. For serum albumin, a typographical error occurred: 2.8 – 3.5 g/dL was erroneously converted into 25-35 g/L.
2: Introduction; 10.16.4: Eligibility Criteria Throughout the protocol	Changes were made in the bosentan eligibility criteria: The requirement for CEC-confirmation of disease progression before study treatment bosentan can be initiated was removed (ie, investigators can initiate study treatment bosentan immediately after reporting a DP event without having to wait for the CEC decision). Consequently, "CEC-confirmed" term was deleted throughout the protocol when referring to study treatment bosentan.	A change was made to allow the initiation of study rescue treatment bosentan for participants with disease progression events prior to the result of the CEC decision about the event.
10.16.12: Safety Assessments	Liver function tests must be performed at ~~monthly~~ **4-week** intervals until one month after study treatment bosentan discontinuation.	To align the windows for the liver and serum pregnancy testing requirements for participants on study treatment bosentan.
1.3.2: Visits and Assessments After Week 12 – for Participants Continuing Double-blind Study Drug Treatment until End of Study, footnote *t*; 1.3.3: Visits and Assessments after EOT – for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study, footnote *bb*; 1.3.4: Visits and Assessments During the Open-Label Extension Period, footnote *ii*; 10.16.12: Safety Assessments; 10.3: Appendix 3: Clinical Laboratory Tests	Pregnancy tests and contraceptive requirements related to study treatment bosentan were clarified: – serum pregnancy tests must be performed every 4 weeks (± 7 days) and not 4 weeks (± 3 days), – serum pregnancy tests and contraception to continue until 30 days after discontinuation of study treatment bosentan, – serum pregnancy test will replace urine tests after initiation of study treatment bosentan, – serum pregnancy tests must be performed in female participants of childbearing potential.	Changes were made to clarify pregnancy tests and contraceptive requirements related to study treatment bosentan. Pregnancy tests must be performed every 4 weeks (± 7 days) and not 4 weeks (± 3 days) to align time window with the monthly liver test window so that both can be done at the same visit.

Section Number and Name	Description of Change	Brief Rationale
4.4: End of Study Definition	A participant will be considered to have completed the double-blind treatment period if he or she has completed all assessments **until the announced end of double-blind treatment period** ~~in October 2024~~ ~~or at premature double-blind study discontinuation in case a positive benefit-risk ratio for selexipag has been demonstrated~~.	Change made to align with current changes in the protocol.
8.2.1.3: Independent CEC Review of Suspected Disease Progression Events	Independent CEC Review of Suspected **Disease Progression** ~~Primary Endpoint~~ Events	To clarify that CEC reviews disease progression events.
1.3.2: Visits and Assessments After Week 12 – for Participants Continuing Double-blind Study Drug Treatment Until End of Study	Analysis Visit for Analyses 1 to 3 / Last DB treatment period Study Visit are to be done at Weeks 16, 24 and 48 for serum NT-proBNP and 6MWD test, and at Weeks 24 and 48 for physical activity/accelerometry, Quality of Life, and echocardiography.	To clarify that if a scheduled visit falls within an analysis visit window, the assessments of the scheduled visit should be performed in addition to the Analysis Visit assessments.
1.1: Synopsis, Objectives and Endpoints; 3: Objectives and Endpoints	A clarification was made to the secondary endpoint: Time to first CEC-confirmed hospitalization ~~and~~**or** death for PAH occurring from Randomization until 7 days after study treatment discontinuation. Consequently, the following was added in the exploratory endpoints: Time to first CEC-confirmed hospitalization for PAH occurring between randomization and until 7 days after study treatment discontinuation.	To clarify this composite endpoint, and to clarify the handling of the components of the "Time to first CEC-confirmed hospitalization or death for PAH occurring from Randomization until 7 days after study treatment discontinuation" composite endpoint.
2.1: Study Rationale; 4.2: Scientific Rationale for Study Design	Ambrisentan was added as an approved treatment for pediatric participants with PAH in addition to sildenafil.	Ambrisentan is approved for pediatric participants with PAH
1.1: Synopsis, Overall Design; 2.3: Benefit/Risk Assessment; 4.1: Overall Design	Pharmacokinetics Final Analysis Report AC-065A203 2022 was added as a reference.	Pharmacokinetics Final Analysis Report AC-065A203 2022 was added as a reference.
1.1: Synopsis	Benefit-risk assessment was added to synopsis. Rationale (including background and hypothesis of the trial), and additional information about trial population were included in Overall design.	Updates were done in the synopsis to align with EU-CTR requirements.
Title Page	EU CTR NUMBER was added.	Change made due to template update.
6.1: Study Interventions Administered; 10.16: Appendix 16: Treatment with Bosentan after PAH-progression: 10.16.5: Study Intervention Administered	Authorization status of selexipag and study treatment bosentan has been added.	Change made due to template update.

Section Number and Name	Description of Change	Brief Rationale
11: References	Following references were added: – new version of selexipag IB, – references referred to in Section 4.2 on NT-proBNP background, – Pharmacokinetics Final Analysis Report AC-065A203 2022, – EMEA guideline on clinical investigations of medical products for the treatment of PAH, – ESC/ERS guidelines for diagnosis and treatment of pulmonary hypertension.	To align with current changes in the protocol.
9: Statistical Considerations; 10.17: Appendix 17: Statistical Analyses for Actelion's Trial of Selexipag in Pediatric with Pulmonary Artery Hypertension	Following sections have been deleted: – Section 9.2.1: Analysis 1, – Section 9.2.2: Analysis 2, – Section 9.2.3: Analysis 3, – Section 9.2.4: Analysis 4, – Section 9.4: Operating Characteristics of the Selected Design, – Appendix 17: Statistical Analyses for Actelion's Trial of Selexipag in Pediatric Patients with Pulmonary Artery Hypertension.	Not applicable due to changes in the protocol.
9.8: Independent Data Monitoring Committee	The following was deleted: The IDMC will review the results of interim analyses performed by the ISSG at Analysis Time point 1 and will provide corresponding recommendations to the sponsor in line with the IDMC charter. The sponsor will further decide taking these recommendations into account.	Not applicable due to changes in the protocol.
10.16.12: Safety Assessments	If a ~~girl~~ **female** becomes pregnant while on bosentan, permanent discontinuation of bosentan treatment must be considered. The investigator must counsel the participant **and, where allowed under local law, her parent(s)/LAR(s)** ~~and her parents/LARs~~ to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.	Change made due to legal requirements in the US.
9.6: Other Analyses	Adjusted least squares means within each treatment group and adjusted estimates of the differences in change from baseline between treatment groups will be displayed for each visit along with their corresponding 2-sided 9~~2~~**5**% CIs.	A typographical error was corrected.
Throughout the protocol	The term "woman" and "girl" were replaced with the term "female".	Change made due to US FDA requirement.
6.3: Measures to Minimize Bias: Randomization and Blinding	Added information for unblinding of study personnel due to a potential safety issue.	Change made due to protocol template update.
10.5.4: Special Reporting Situations	**Participant-specific** ~~S~~**s**pecial reporting situations should be recorded in the CRF.	Change made due to protocol template update.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made, as well as minor changes for clarification.	Minor errors were corrected, and minor changes were made for clarification

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Period to Assess the Efficacy and Safety of Selexipag as Add-On Treatment to Standard of Care in Children Aged ≥2 to <18 years with Pulmonary Arterial Hypertension

Selexipag (JNJ-67896049) is an orally available, selective, and long-acting non-prostanoid agonist of the prostacyclin receptor approved and commercially available for the treatment of adult patients with pulmonary arterial hypertension (PAH) in the United States, the European Union, Japan, and other countries/territories. For the most comprehensive nonclinical and clinical information regarding selexipag, refer to the latest version of the Investigator's Brochure (Selexipag IB). Selexipag was approved in the United States in December 2015 (brand name: UPTRAVI® [Uptravi® USPI]), and in Europe in May 2016 (Uptravi® SmPC).

BENEFIT-RISK ASSESSMENT

The potential risks of participation in the study include exposure to study intervention with the potential for side effects, and the inherent risks associated with venipuncture and blood sample collections. The study has been designed to minimize these inherent risk factors by keeping blood sampling procedures to a minimum and including efficacy assessments that are non-invasive.

The primary ethical concern is the use of placebo as a comparator. In the setting of this study, the use of placebo is considered acceptable because the inclusion criteria require the presence of at least 1 allowed PAH-related concomitant therapy (PDE-5 inhibitor, and/or endothelin receptor antagonist [ERA]). In addition, the study provides rescue study medication bosentan to patient not treated with ERA at baseline with PAH disease progression event.

Uptravi (selexipag) is a selective IP receptor agonist for oral use with PK characteristics suitable for bid dosing and with proven efficacy and safety in adults with PAH. The known similarities between PAH disease in adult and pediatric patients suggest that pediatric PAH patients could benefit from selexipag treatment, and the tolerability and safety profile of selexipag administered to children is expected to be consistent with that of adult patients. The benefit of medicines acting on the prostacyclin pathway (IP receptor agonists) in the treatment of PAH in adults is established, as acknowledged by current treatment guidelines. To date, selexipag is the only orally available IP receptor agonist approved globally for long-term treatment across WHO FC II-III, primarily in combination with current first-line oral PAH-specific medicines, in adult patients in need of additional therapy because of insufficient disease control. Uptravi represents an important additional treatment option for these patients.

Currently, no medicines targeting the prostacyclin pathway are approved for pediatric use in PAH.

Based on the measures taken in this study to minimize the risks to pediatric patients, the potential benefits of study participation outweigh the associated risks.

OBJECTIVES AND ENDPOINTS

Primary	
• To evaluate whether the addition of selexipag to Standard of Care treatment delays disease progression in children with pulmonary arterial hypertension in comparison to placebo.	• Time to disease progression from randomization up to 7 days after study treatment discontinuation. Disease progression will be adjudicated by a blinded Clinical Event Committee and is defined as the first occurrence of either of the following components: – Death (all causes) – Atrial septostomy or Potts' anastomosis, or registration on lung transplant list – Hospitalization due to worsening pulmonary arterial hypertension[a] – Clinical worsening of pulmonary arterial hypertension defined as: Need for, or initiation of new pulmonary arterial hypertension-specific therapy[b] or intravenous diuretics or continuous oxygen use AND at least one of the following: o Worsening in World Health Organization functional class, or o New occurrence or worsening of syncope (in frequency or severity as per medical judgment), or o New occurrence or worsening of at least two pulmonary arterial hypertension symptoms, ie, shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue), or o New occurrence or worsening of signs of right heart failure not responding to oral diuretics. Investigators will document the condition of the participant at baseline (narrative and echocardiography). In the presence of disease progression, the investigator will prepare a narrative of the participant's condition, perform an echocardiography, and test the level of N-terminal pro-brain natriuretic peptide (NT-proBNP) to document disease progression. These data, together with relevant electronic Case Report Form data and any other relevant supportive routine assessment (eg, right heart catheterization, magnetic resonance imaging, uric acid, etc) and potential hospital discharge summary (if applicable),

[a] Excluding hospitalizations that are elective, routine, or clearly attributable to the appearance/worsening of comorbidities (eg, pneumonia).

[b] eg, Endothelin receptor antagonist, phosphodiesterase type-5 inhibitor, prostanoids, soluble guanylate cyclase stimulator.

	will be provided to the Clinical Event Committee for adjudication. Data on adverse events specific to prostanoids (eg, jaw pain) will not be provided to the Clinical Event Committee to keep them blinded. The Clinical Event Committee will determine the components of the event, the relationship of hospitalization with pulmonary arterial hypertension, and the event onset date. If there is a missing assessment (eg, no World Health Organization functional class), the Clinical Event Committee will ultimately be responsible for qualifying or disqualifying the event and the date of the event for the analysis of the primary endpoint, using all available clinical data.
Secondary	
• To evaluate whether the addition of selexipag to Standard of Care treatment decreases NT-proBNP in children with pulmonary arterial hypertension in comparison to placebo.	• Change in $\log_2$(NT-proBNP) from baseline to Week 24 ($\log_2$(Week 24/Baseline)).
• To assess the safety and tolerability of selexipag in children with pulmonary arterial hypertension.	• Treatment-emergent adverse events and serious adverse events. • Adverse events leading to premature discontinuation of study treatment. • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points. • Growth: Change in body weight and height from baseline to all assessed time points. • Sexual maturation (Tanner stage) change from baseline to all assessed time points up to 3 days after study treatment discontinuation. • Treatment-emergent electrocardiogram abnormalities. • Treatment-emergent marked laboratory abnormalities at each time point of assessment. • Treatment-emergent change from baseline in thyroid stimulating hormone over time. • Treatment-emergent change in selected laboratory variables from baseline to all assessed time points.

	A treatment-emergent event or abnormality is temporally associated with the use of study treatment whether or not considered by the investigator as related to study treatment.
• To evaluate whether selexipag can delay hospitalization and death due to pulmonary arterial hypertension worsening in children.	• Time to first Clinical Event Committee-confirmed hospitalization or death due to pulmonary arterial hypertension occurring from Randomization until 7 days after study treatment discontinuation. The Clinical Event Committee will determine the relationship of death and hospitalization with pulmonary arterial hypertension and the event onset date.
• To assess the trough plasma concentrations of selexipag and its active metabolite at steady state in children with pulmonary arterial hypertension.	• Trough plasma concentration at steady-state of selexipag and its metabolite ACT-333679 collected during the maintenance period.
Exploratory	
• To explore the following safety and efficacy variables.	• Time to death (all causes) occurring between Randomization and the Analysis Visit for each Analysis. • Time to first Clinical Event Committee-confirmed hospitalization for PAH occurring between randomization and until 7 days after study treatment discontinuation. • Time to first Clinical Event Committee-confirmed death due to pulmonary arterial hypertension occurring from randomization until 7 days after study treatment discontinuation. • Time to Clinical Event Committee-confirmed disease progression up to the Analysis Visit for each Analysis. • World Health Organization functional class III/IV (yes/no) at each time point of assessment up to 7 days after study treatment discontinuation. • Change in World Health Organization functional class from baseline/enrollment to each time point of assessment up to 7 days after study treatment discontinuation. • Change from baseline to each time point of assessment in exercise capacity up to 7 days after study treatment discontinuation as measured by the 6-minute walk distance in children ≥6 years of age who are developmentally able to understand and perform the test.

	• Change in physical activity (measured by accelerometry) from baseline to 1 year (48 weeks) after Randomization. • Change in Panama functional class from baseline to each time point of assessment up to 7 days after study treatment discontinuation. • Percent of baseline in serum NT-proBNP at each time point of assessment up to 7 days after study treatment discontinuation. • Change from baseline in echocardiographic variables (imaging and Doppler evaluation) such as right ventricular systolic pressure, tricuspid annular plane systolic excursion, etc, at each time point of assessment up to 7 days after study treatment discontinuation. • Time to clinical worsening from randomization up to 7 days after study treatment discontinuation, where clinical worsening is defined as at least one of the following components (adapted from the CHMP definition [EMEA 2008]): 1. All-cause death. 2. Non-planned pulmonary arterial hypertension related hospitalization. 3. Pulmonary arterial hypertension-related deterioration identified by at least one of the following parameters: i. increase in World Health Organization functional class, ii. deterioration in exercise testing (15% decrease from baseline in 6-minute walk distance), iii. new or worsening signs or symptoms of right-side heart failure.

• To explore the Quality of Life.	In a subset of countries/territories, change from baseline to all time points of assessments in: • Quality of Life as measured by the PedsQL™ 4.0 Generic Core Scales Short Form • Quality of Life as measured by the disease-specific PedsQL™ 3.0 Cardiac Module using the "heart problems and treatment" component only. • Quality of Life as measured by the PedsQL™ Multidimensional Fatigue Scale standard version using the "general fatigue" component only. Each of these endpoints will be analyzed as assessed by participants and as assessed by a caregiver (ie, parent or legally acceptable representative [LAR]). Questionnaires are adapted for the following age categories: • Toddlers: 2 to 4 years of age • Young children: 5 to 7 years of age • Children: 8 to 12 years of age • Adolescents: 13 to 18 years of age For the youngest age category (toddlers) the questionnaire exists only for parent(s) or LAR(s), ie, Parent report). Young children will be interviewed by a site staff member. For the two oldest age categories, separate questionnaires exist for parent(s) or LAR(s) and for participants (ie, Child report) and address the same items.
• Other.	• Palatability of the study intervention at Week 4, Week 12, and End of Treatment, assessed using a 5-point facial hedonic scale. • Acceptability of the study intervention at Week 4, Week 12, and End of Treatment, as assessed through a 3-point categorical scale as to whether the child swallowed the medication.
Exploratory – Open-Label Period	
• To explore the long-term safety, tolerability, and efficacy of selexipag in children with pulmonary arterial hypertension.	**Tolerability/Safety** • Treatment-emergent adverse events and serious adverse events. • Adverse events leading to discontinuation of study treatment.

	• Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points. • Growth: Change in body weight and height from baseline to all assessed time points. • Sexual maturation (Tanner stage) from baseline to all assessed time points up to 3 days after study treatment discontinuation. • Treatment-emergent electrocardiogram abnormalities. • Treatment-emergent marked laboratory abnormalities at each time point of assessment. • Treatment-emergent change from baseline in thyroid stimulating hormone over time. • Treatment-emergent change in selected laboratory variables from baseline to all assessed time points. A treatment-emergent event or abnormality is temporally associated with the use of study treatment whether or not considered by the investigator as related to study treatment. **Efficacy** • Change in modified New York Heart Association/World Health Organization functional class from the date of first dose in the OLEP to each time point of assessment up to 7 days after study treatment discontinuation. • Change in Panama functional class from the date of first dose in the OLEP to each time point of assessment up to 7 days after study treatment discontinuation. • Time to (investigator assessed) disease progression from the date of first dose in the OLEP up to 7 days after study treatment discontinuation.

Hypothesis

The primary hypothesis of this study is that selexipag reduces the risk of disease progression (measured as time from randomization to first Clinical Event Committee (CEC) – confirmed disease progression event) compared to placebo, in pediatric participants with pulmonary arterial hypertension.

OVERALL DESIGN

Given the significant medical need to develop treatments in children with PAH, further clinical studies in the pediatric population are needed to provide more data for the management of PAH in children.

The pediatric development plan of selexipag consists of a Phase 2 study (AC-065A203) to establish the selexipag dose(s) and determine the pharmacokinetics (PK) of selexipag and its active metabolite in children, followed by this current Phase 3 study to assess the efficacy, safety, and tolerability of selexipag in this population based on the dosing recommendation established in AC-065A203.

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group study with open-label extension period to assess the efficacy and safety of selexipag as add-on to standard of care in children aged ≥2 to <18 years with pulmonary arterial hypertension (WHO Group 1).

The study consists of a screening period of up to 6 weeks and a double-blind treatment period, including uptitration and maintenance periods, followed by a 3-year open-label extension period and a 30-day Safety Follow-up Period that occurs after the last dose of study intervention (either double-blind or open-label).

Enrollment will start with study participants in age cohorts 1 (≥12 to <18 years of age) and 2 (≥6 to <12 years of age), ie, those age groups for whom the dosing was confirmed in the pediatric Phase 2 study AC-065A203 (PK Interim Analysis Report-1 AC-065A203 2019 and PK Interim Analysis Report-2 AC-065A203 2020). Enrollment into age cohort 3 (≥2 to <6 years of age) will be initiated after the starting dose and uptitration regimen are confirmed in the corresponding age cohort of AC-065A203 (PK Final Analysis Report AC-065A203 2022). Results of the dosing confirmation are documented in interim and final pharmacokinetic analysis reports. If the dosing has to be adjusted based on emerging data for age cohort 3, the protocol will be amended accordingly.

Participants will be centrally randomized via an interactive web response system in a 1:1 ratio to either selexipag or placebo. Treatment allocation will be stratified by World Health Organization functional class (II vs III), and for presence of background pulmonary arterial hypertension specific treatment (monotherapy vs combination therapy) at baseline.

Participants who complete the double-blind treatment period will be offered the option to continue in the open-label extension period for 3 years, followed by the Safety Follow-up Period.

Participants who have CEC-confirmed pulmonary arterial hypertension disease progression will remain on double-blind treatment and enter the Post Event Treatment Period and will be offered the option to continue into the open-label extension period and 30-day Safety Follow-up Period.

Participants who prematurely discontinue double-blind treatment will have an End of Treatment visit and enter the Safety Follow-up and Post-Treatment Observation Periods. Participants who withdraw consent from the study will have an End of Treatment visit and enter the Safety Follow-up Period; survival status follow-up information will be collected from these participants.

The duration of the double-blind treatment period will be different for individual participants and will depend on the time of study entry.

Approximately 125 participants are expected to be randomized in the double-blind treatment period. Within the study, 4 analysis timepoints are planned CCI [redacted]

- Analysis 1 CCI [redacted] will be performed with a data cutoff date when at least 80 participants have been treated and followed up for at least 24 weeks in the double-blind treatment period.
- Analysis 2 CCI [redacted] will be performed with a data cutoff date when approximately 125 participants have been followed up for at least 24 weeks or prematurely discontinued the study in the double-blind treatment period.
- Analysis 3 is CCI [redacted] at the end of the double-blind treatment period after all participants included in Analysis 2 have completed their EOT visit.
- Analysis 4 is the analysis of the OLEP after all participants have completed the 3-year OLEP or have prematurely discontinued the study.

Within 6 weeks of the announcement of each analysis by the Sponsor, Analysis Visits will be scheduled for all participants. Data collected during the Analysis Visits will be included in the respective analyses.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

A target of approximately 125 participants will be randomly assigned in this study during the double-blind treatment period.

INTERVENTION GROUPS AND DURATION

Study participation in the double-blind treatment period for each participant will last until approximately 125 participants are followed up for at least 24 weeks in the double-blind treatment period and for an additional 3 years in the optional open-label extension. Eligible participants will be randomly assigned to receive selexipag or placebo administered orally bid approximately every 12 hours for the duration of the double-blind treatment period.

The starting dose of selexipag will be based on the participant's body-weight category. The body-weight category, starting dose, and uptitration scheme determined at baseline/enrollment should be kept unchanged until Week 16 (downtitration for safety/tolerability reasons is permitted). After Week 16, if the body-weight category of the participant changes, study intervention can be uptitrated further or downtitrated to the corresponding dose level of the actual body-weight category, as deemed appropriate by the investigator (if dose levels overlap between body-weight categories, the dose level may also remain stable).

In addition, irrespective of whether the body-weight category changes or not, after Week 16, investigators will be allowed to change the participants' study intervention dose further if needed (up to the maximum allowed dose based on body-weight category).

Selexipag and matching placebo are supplied by the sponsor in child-proof bottles containing tablets with the following dosage strengths:

- Bottles of 120 film-coated tablets containing 200 μg of selexipag or matching placebo.
- Bottles of 280 film-coated mini-tablets containing 50 μg of selexipag or matching placebo.

Two additional mini-tablet dosage strengths will be rolled out during the study: 100 μg and 150 μg mini-tablets will replace the concept of combining 50 μg mini-tablets and 200 μg tablets for the body-weight groups ≥9 to <25 kg and ≥25 to <50 kg, respectively:

- Bottles of 280 film-coated mini-tablets containing 100 mg of selexipag or matching placebo.
- Bottles of 280 film-coated mini-tablets containing 150 mg of selexipag or matching placebo.

These additional mini-tablet strengths will become available in participating countries/territories in a staggered approach depending on availability of region-specific stability data.

Study intervention will be labeled to comply with the applicable laws and regulations of the countries/territories in which the study sites are located.

EFFICACY EVALUATIONS

Efficacy will be assessed by the monitoring of disease progression, creation of participant narratives by the investigator, verifying signs and symptoms of pulmonary arterial hypertension, independent Clinical Event Committee review of suspected primary endpoint events, the Panama Functional Class, the World Health Organization functional class, NT-proBNP serum levels, echocardiography, physical activity/accelerometry, 6-minute walk test, and survival follow-up.

Quality of life will be assessed using The Peds QL™ Pediatric Quality of Life Inventory version 4.0 short form to assess general physical, emotional, social and school functioning (15 questions).

The "heart problems and treatment" component of the Peds QL™ Cardiac Module version 3.0 and the "general fatigue" component of the Peds QL™ Multidimensional Fatigue Scale standard version questionnaires will assess heart problems and problems with treatment (7 questions) and problems with general fatigue (6 questions).

OTHER EVALUATIONS

Acceptability will be assessed using a 3-point categorical scale and palatability will be assessed using a 5-point facial hedonic scale.

PHARMACOKINETIC EVALUATIONS

Plasma samples will be used to evaluate the pharmacokinetics of selexipag (JNJ-67896049) and its metabolite ACT-333679 (JNJ-68006861) using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method under the supervision of the sponsor. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

SAFETY EVALUATIONS

Safety will be assessed by the monitoring of adverse events, physical examinations (including weight and height), vital sign measurements, clinical laboratory tests (including pregnancy tests, if applicable), electrocardiograms, and Tanner stage.

STATISTICAL METHODS

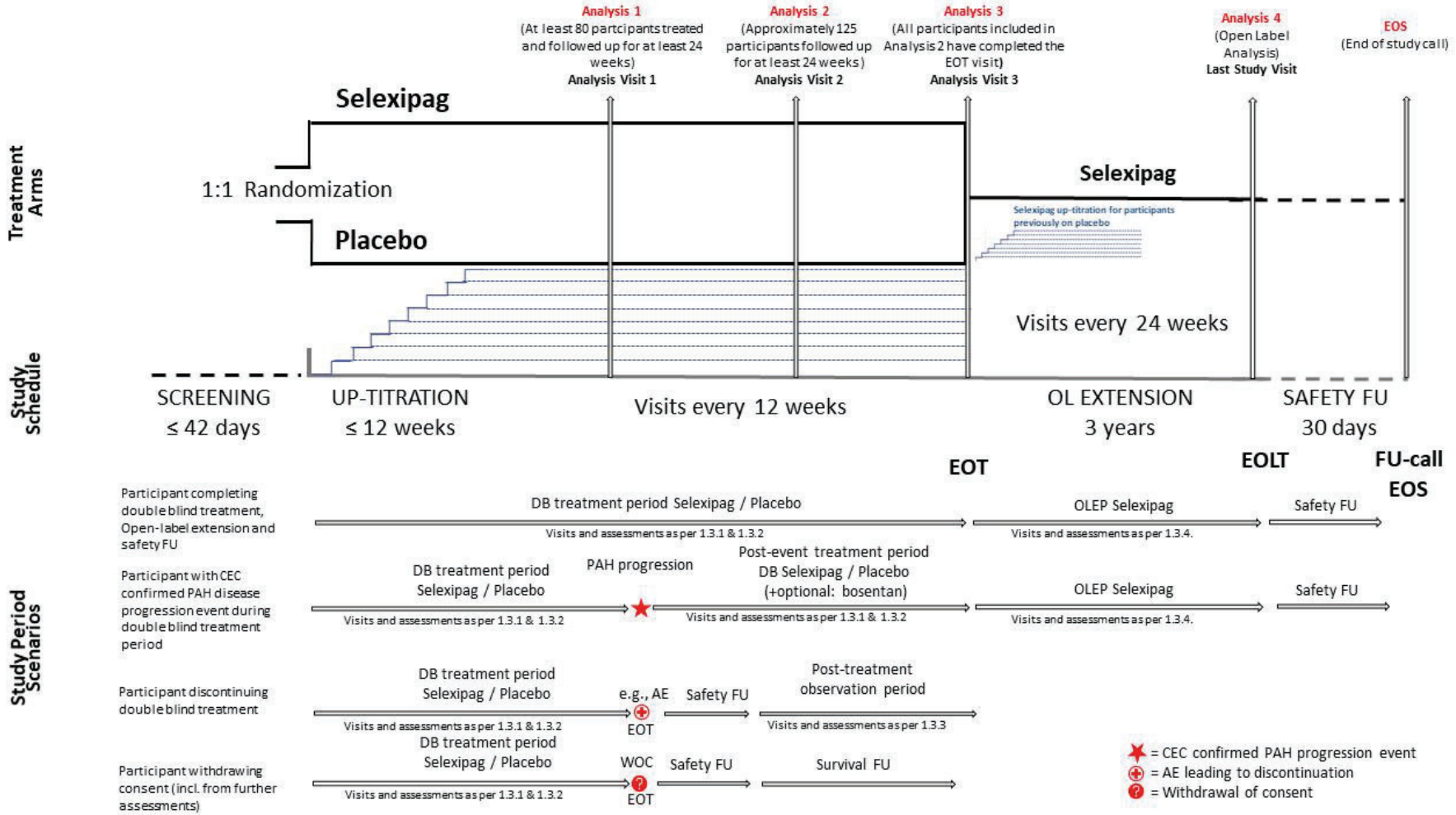
Sample Size Determination

For the CCI [redacted] (Analysis 1), the sample size is not based on formal statistical considerations.

For the CCI [redacted] (Analysis 2), the sample size of approximately 125 participants is chosen for NT-proBNP change from baseline to Week 24 assessment CCI [redacted]

1.2. Schema

Figure 1: Schematic Overview of the Study



AE = adverse event; CEC = Clinical Event Committee; DB = double-blind; EOLT = End of Open-Label Treatment; EOS = End of Study; EOT = End of Treatment; FU = follow-up; OL = open-label; OLEP = open-label extension period; PAH = pulmonary arterial hypertension; WOC = withdrawal of consent.

1.3. Schedule of Activities (SoA)

1.3.1. Visit and Assessment Schedule During Double-blind Treatment Period Uptitration Period Until Week 12

Period	Screening	Baseline/ enrollment	Double-blind Treatment Period: Uptitration											
Name	Visit 1	Visit 2	Tel. call	Tel. call	Tel. call	Visit 3	Tel. call	Tel. call	Tel. call	Visit 4	Tel. call	Tel. call	Tel. call	Visit 5
Time	≤42 days before Day 1	Day 1 [c]	Week 1[d] ±3 d	Week 2 ±3 d	Week 3 ±3 d	Week 4 ±3 d	Week 5 ±3 d	Week 6 ±3 d	Week 7 ±3 d	Week 8 ±3 d	Week 9 ±3 d	Week 10 ±3 d	Week 11 ±3 d	Week 12 ±3 d
Screening/Administrative														
Informed consent/assent[e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Review medical history requirements	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Review PAH-related treatments and interventions	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility	X	X	-	-	-	-	-	-	-	-	-	-	-	-
Baseline Characteristics Adjudication[f]	X PAH-CHD only	-	-	-	-	-	-	-	-	-	-	-	-	-
Study Intervention Administration														
Study intervention dispensing[g]	-	X	-	-	-	-	-	-	-	-	-	-	-	X
Study intervention return	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Palatability of study intervention	-	-	-	-	-	X	-	-	-	-	-	-	-	X
Acceptability of study intervention	-	-	-	-	-	X	-	-	-	-	-	-	-	X
First dose of study intervention		X (pm)	-	-	-	-	-	-	-	-	-	-	-	-
Dose titration	-	-	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	X (pm)	-
Efficacy Assessments														
Serum NT-proBNP	-	X	-	-	-	-	-	-	-	-	-	-	-	-
PAH signs/symptoms	X	X	-	-	-	X	-	-	-	X	-	-	-	X
WHO Functional Class	X	X	-	-	-	X	-	-	-	X	-	-	-	X
Panama FC	X	X	-	-	-	X	-	-	-	X	-	-	-	X
Participant narrative	-	X	-	-	-	-	-	-	-	-	-	-	-	-

[c] An overnight stay leading to Day 1 may be considered for logistical reasons

[d] 1 week is equal to 7 days

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

[f] For participants with PAH with coincidental CHD relevant clinical, RHC and echocardiography data must be submitted to the BCAC to confirm eligibility.

[g] Includes accountability at study intervention return.

Period	Screening	Baseline/ enrollment	Double-blind Treatment Period: Uptitration											
Name	**Visit 1**	**Visit 2**	Tel. call	Tel. call	Tel. call	**Visit 3**	Tel. call	Tel. call	Tel. call	**Visit 4**	Tel. call	Tel. call	Tel. call	**Visit 5**
Time	≤42 days before Day 1	**Day 1** [e]	Week 1[d] ±3 d	Week 2 ±3 d	Week 3 ±3 d	**Week 4 ±3 d**	Week 5 ±3 d	Week 6 ±3 d	Week 7 ±3 d	**Week 8 ±3 d**	Week 9 ±3 d	Week 10 ±3 d	Week 11 ±3 d	**Week 12 ±3 d**
6MWD test[h]	-	X	-	-	-	-	-	-	-	-	-	-	-	-
Physical activity/Accelerometry[i]	X	-	-	-	-	-	-	-	-	-	-	-	-	X
Quality of Life	-	X	-	-	-	-	-	-	-	-	-	-	-	X
Echocardiography	X	-	-	-	-	-	-	-	-	-	-	-	-	X
Disease progression[j]	-	-	-	-	-	X	-	-	-	X	-	-	-	X
Safety Assessments														
Physical examination	X	X	-	-	-	X	-	-	-	X	-	-	-	X
Weight and height	X	X	-	-	-	-	-	-	-	-	-	-	-	X
Vital signs (BP, heart rate)	X	X	-	-	-	X	-	-	-	X	-	-	-	X
ECG	-	X	-	-	-	X	-	-	-	-	-	-	-	X
Tanner stage[k]	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Laboratory Tests														
Hematology & chemistry	X	X	-	-	-	X	-	-	-	-	-	-	-	X
Thyroid markers[l]	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Pregnancy test (if appl.)[m]	X	X	-	-	-	X	-	-	-	X	-	-	-	X
Ongoing participant review														
Concomitant therapy or intervention	X	X	-	-	-	X	-	-	-	X	-	-	-	X
Childbearing potential[n]	X	X	-	-	-	X	-	-	-	X	-	-	-	X
SAEs/AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X

6MWD = 6-minute walk distance; AE = adverse event; BCAC = Baseline Characteristics Adjudication Committee; BP = blood pressure; ECG = electrocardiogram; NT-proBNP = N terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-CHD = PAH-congenital heart disease; RHC = right heart catheterization; SAE = serious adverse event; TSH = thyroid stimulating hormone; WHO = World Health Organization.

h 6MWD in children ≥6 to <18 years of age who can understand and perform the test correctly.

i To be assessed at any time between Visit 1 and Visit 2 and during the 10-14 consecutive days before Visit 5/Week 12.

j In the case of suspected PAH progression during a scheduled visit, all assessments required to evaluate suspected disease progression as mentioned in Section 1.3.2. should be performed.

k Tanner stage can be reported through a self-assessment by the participant.

l TSH will be assessed at each time point, except Visit 1 (screening); thyroid antibodies will be assessed at Visit 2 and thereafter only when medically indicated; Free T3 and free T4 will be assessed in case TSH is abnormal or when medically indicated.

m Serum pregnancy test to be performed at screening and urine pregnancy tests every 4 weeks ± 3 days in all female participants of childbearing potential.

n Parents and participants will be asked to contact the investigator immediately if the participant has her first menstrual bleed or becomes sexually active between study visits.

1.3.2. Visits and Assessments After Week 12 – for Participants Continuing Double-blind Study Drug Treatment Until End of Study

Period	Double-blind Treatment Period: Maintenance					Safety Follow-up Period
Name	Scheduled Visits		Unscheduled Visits	Suspected PAH Disease progression	Analysis Visit for Analyses 1 to 3[o] / Last DB treatment period Study Visit	End of Study
Number	Visit 6	Visit 7, 8, 9, 10, …	U1, U2, U3, ...	DP 1, 2, ...	LSV	EOS call
Time	Week 16 ±3 days	Week 24 and every 12 weeks thereafter ±2 weeks	If medically indicated	In case of PAH worsening +5 days of suspected progression[p]	≤6 weeks after announcing the analysis	30 days after last study drug dose (+7 days)
Study Intervention Administration						
Study intervention dispensing	X	X	-	-	X	-
Study intervention return	X	X	-	-	X	-
Efficacy Assessments						
Serum NT-proBNP	X	Weeks 24 & 48	If indicated	X	Weeks 16 & 24 & 48	-
PAH signs/symptoms	X	X	If indicated	X	X	-
WHO Functional Class	X	X	If indicated	X	X	-
Panama FC	X	X	If indicated	X	X	-
Participant narrative	-	-	If indicated	X	-	-
6MWD test[q]	X	Weeks 24 & 48	If indicated	X	Weeks 16 & 24 & 48	-
Physical activity/Accelerometry	-	Weeks 24 & 48	-	-	Weeks 24 & 48	-
Quality of Life	-	Weeks 24 & 48	If indicated	X	Weeks 24 & 48	-
Echocardiography	-	Weeks 24 & 48	If indicated	X	Weeks 24 & 48	-
Disease progression[r]	X	X	X	-	X	
CEC adjudication of suspected disease progression	-	-	-	X	-	-
Safety Assessments						
Physical examination	X	X	If indicated	X	X	-
Weight and height	X	X	If indicated	-	X	-
Vital signs (BP, heart rate)	X	X	If indicated	X	X	-
ECG	X	X	If indicated	X	X	-
Tanner stage[s]	-	X	If indicated	-	X	X

[o] As defined in Section 9.2.

[p] Regardless of CEC-confirmed disease progression, participants will continue double-blind study intervention. Optional rescue treatment with bosentan may be initiated. Initiation of any prostanoid must lead to the discontinuation of double-blind treatment.

[q] 6MWD in participants of ≥6 to <18 years of age who are able to understand and perform the test correctly.

[r] In the case of suspected PAH-progression during a scheduled visit, the assessments in column "Disease progression" are to be performed.

[s] Starting with Week 24, Tanner stage will be assessed every 24 weeks and can be reported through self-assessment by the participant.

Period	Double-blind Treatment Period: Maintenance					Safety Follow-up Period
Name	Scheduled Visits		Unscheduled Visits	Suspected PAH Disease progression	Analysis Visit for Analyses 1 to 3[o] / Last DB treatment period Study Visit	End of Study
Number	Visit 6	Visit 7, 8, 9, 10, …	U1, U2, U3, ...	DP 1, 2, ...	LSV	EOS call
Time	Week 16 ±3 days	Week 24 and every 12 weeks thereafter ±2 weeks	If medically indicated	In case of PAH worsening +5 days of suspected progression[p]	≤6 weeks after announcing the analysis	30 days after last study drug dose (+7 days)
Clinical Laboratory Tests						
Hematology & Chemistry	X	X[t]	If indicated	X	X	-
Thyroid markers[u]	X	X	If indicated	X	X	-
Pregnancy test (if appl.)	Urine tests in female participants of childbearing potential every 4 weeks ± 3 days					X
Ongoing Participant Review						
Concomitant therapy or intervention	X	X	If indicated	X	X	-
Childbearing potential	X	X	If indicated	-	X	-
SAEs/AEs	X	X	If indicated	X	X	X
Pharmacokinetics						
PK sampling[v]	X (twice at steady state)		-	-	-	-

6MWD = 6-minute walk distance; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CEC = Clinical Event Committee; DB = double-blind; DP = Disease progression; ECG = electrocardiogram; EOS = end of study; FC = functional class; LSV = last study visit; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WHO = World Health Organization.

[t] If participants initiate bosentan rescue treatment under this protocol following PAH disease progression, 4-weekly (±7 days) liver function tests (ALT, AST, alkaline phosphatase, total & direct bilirubin) and hemoglobin (every 4-weeks during the first 4 months of treatment, and quarterly thereafter) need to be performed in addition. Prior to initiation of bosentan treatment, and thereafter every 4 weeks ±7 days, a negative serum pregnancy test is required in female participants of childbearing potential.

[u] TSH will be assessed at each time point; thyroid antibodies will be assessed when medically indicated; Free T3 and Free T4 will be assessed in case TSH is abnormal or when medically indicated.

[v] Trough PK sample will be collected at two (any) visits during steady-state. Participants should take their morning dose of study drug at site after collection of the PK sample during these visits.

1.3.3. Visits and Assessments after EOT – for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study

Period		Post Treatment Observation Period					
Name	End of double-blind Treatment	Safety Follow-up Period	Scheduled Visits	Unscheduled Visits	Disease progression	Survival Follow-Up[w]	End of Study
Number	EOT	Safety FU call	PT V1, 2, 3,…	PT U1, U2, ...	PT DP 1, 2, ...	SFU1, SFU2	EOS
Time	Up to 10 days after last study drug dose	30 days after last study drug dose (+7 days)	every 24 weeks ±2 weeks	If medically indicated	In case of PAH worsening +5 days of suspected progression	At least yearly	≤6 weeks after announcing study closure
Study Intervention Administration							
Study intervention dispensing[x]	X	-	X		-	-	-
Study intervention return	X	-	X				X
Palatability and acceptability of selexipag	X	-	-	-	-	-	-
Efficacy assessments							
Serum NT-proBNP	X	-	-	-	X	-	-
PAH signs/symptoms	X	-	X	X	X	-	X
WHO Functional Class	X	-	X	X	X	-	X
Panama FC	X	-	X	X	X		X
6MWD test[y]	X	-	-	-	X	-	-
Quality of life	X	-	-	-	-	-	-
Echocardiography	X	-	-	X	X	-	-
Disease progression[z]	X	-	X	X	-	-	X
CEC adjudication of suspected disease progression	-	-	-	-	X	-	-
Safety assessments							
Physical examination	X	-	-	-	X	-	-
Weight and height	X	-	X	-	-	-	X
Vital signs (BP, heart rate)	X	-	X	X	X	-	X
ECG	X	-	-	-	-	-	-
Tanner stage[aa]	X	-	X	-	-	-	X

[w] Participants who disagree to continue study visits after end of study intervention treatment will be followed at least yearly to collect survival data.

[x] Only applicable for patients receiving bosentan rescue treatment following PAH progression.

[y] 6MWD in participants of ≥6 to <18 years of age who are able to understand and perform the test correctly.

[z] In the case of suspected PAH-progression the assessments in column "Disease progression" are to be performed.

[aa] Tanner stage will be assessed at every other visit (ie, every 48 weeks) and can be reported through self-assessment by the participant.

Period		Post Treatment Observation Period					
Name	**End of double-blind Treatment**	**Safety Follow-up Period**	**Scheduled Visits**	**Unscheduled Visits**	**Disease progression**	**Survival Follow-Up[w]**	**End of Study**
Number	**EOT**	**Safety FU call**	**PT V1, 2, 3,…**	**PT U1, U2, ...**	**PT DP 1, 2, ...**	**SFU1, SFU2**	**EOS**
Time	Up to 10 days after last study drug dose	30 days after last study drug dose (+7 days)	every 24 weeks ±2 weeks	If medically indicated	In case of PAH worsening +5 days of suspected progression	At least yearly	≤6 weeks after announcing study closure
Clinical Laboratory Tests							
Hematology & Chemistry[bb]	X	-	-	-	-	-	-
Pregnancy test (if appl.)		Urine tests in female participants of childbearing potential every 4 weeks ± 3 days[cc]					
Ongoing Participant Review							
Concomitant therapy or intervention	X	-	X	X	X	PAH-spec. therapies	X
Childbearing potential	X	-	X	-	-	-	X
SAEs/AEs	X	X	X	X	X	-	X
Vital Status	-	-	-	-	-	X	X[dd]

6MWD = 6-minute walk distance; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CEC = Clinical Event Committee; ECG = electrocardiogram; EOS = end of study; EOT = End of Treatment; FC = functional class; FU = follow-up; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; SAE = serious adverse event; SFU = survival follow-up; WHO = World Health Organization.

[bb] If participants initiate bosentan rescue treatment under this protocol following PAH disease progression, 4-weekly (±7 days) liver function tests (ALT, AST, alkaline phosphatase, total & direct bilirubin) and hemoglobin (every 4-weeks during the first 4 months of treatment, and quarterly thereafter) need to be performed in addition. Prior to initiation of bosentan treatment, and thereafter every 4 weeks ± 7 days, a negative serum pregnancy test is required in female participants of childbearing potential.

[cc] Last pregnancy test must be performed 30 days after last study intervention (placebo/selexipag) and treatment with bosentan, if applicable.

[dd] Participants in survival follow-up period at time of announcement of study closure will be contacted within 6 weeks to assess vital status.

1.3.4. Visits and Assessments During the Open-Label Extension Period

Participants will be offered the option to participate in the open-label extension period only after a positive benefit-risk ratio in children with PAH was confirmed.

Period	Treatment Period: Open-Label Extension Period					Safety Follow-up Period[ee]
Name	Scheduled Visits		Unscheduled Visits	Disease progression	Last Study Visit	End of Study
Number	OL 1, 2, 3, …	OL – iMTD	OL U1, U2, ...	OL DP 1, 2, ...	LSV	EOS call
Time	every 24 weeks[ff] ±2 weeks	Week 12 ±3 days – Only applies to participants previously on placebo and initiating treatment with selexipag	If medically indicated	In case of PAH worsening +5 days of suspected progression	≤6 weeks after announcing study closure	30 days after last study drug dose (+7 days)
Study Intervention Administration						
Study intervention dispensing[gg]	X	X	-	-	-	-
Study intervention return	X	X	-	-	X	-
Efficacy Assessments						
PAH signs/symptoms	X	X	X	X	X	-
WHO Functional Class	X	X	X	X	X	-
Panama FC	X	X	X	X	X	-
Safety Assessments						
Physical examination	X	X	-	-	X	-
Weight and height	X	X	-	-	X	-
Vital signs (BP, heart rate)	X	X	-	X	X	-
ECG	X	X	-	-	X	-
Tanner stage[hh]	X	X	-	-	X	-

[ee] For participants who complete OLEP and who are eligible for a PTA program or open-label study for long-term follow-up (see Section 6.8), the safety follow-up period will be waived and the EOS call is defined as the end of OL treatment at the LSV.

[ff] Participants transitioning from placebo treatment to treatment with selexipag after unblinding will uptitrate selexipag as described for initial study entry, ie, the site staff will call the participant weekly. Also, there will be a visit at Week 12 to assess the iMTD before selexipag is dispensed again. This is not required for participants who were treated with selexipag during the study. Participants who discontinued double-blind treatment previously cannot be included in the OLEP.

[gg] Selexipag and bosentan (if applicable, see o). Participants previously on placebo will uptitrate selexipag from the starting dose corresponding to their body-weight group as described in Section 6.1.

[hh] Tanner stage will be assessed at every other visit (ie, every 24 weeks) and can be reported through self-assessment by the participant.

Period	Treatment Period: Open-Label Extension Period					Safety Follow-up Period[ee]
Name	Scheduled Visits		Unscheduled Visits	Disease progression	Last Study Visit	End of Study
Number	OL 1, 2, 3, …	OL – iMTD	OL U1, U2, ...	OL DP 1, 2, ...	LSV	EOS call
Time	every 24 weeks[ff] ±2 weeks	Week 12 ±3 days – Only applies to participants previously on placebo and initiating treatment with selexipag	If medically indicated	In case of PAH worsening +5 days of suspected progression	≤6 weeks after announcing study closure	30 days after last study drug dose (+7 days)
Clinical Laboratory Tests						
Hematology & Chemistry[ii]	X	X	If indicated	-	X	-
Pregnancy test (if appl.)	Urine tests in female participants of childbearing potential every 4 weeks ± 3 days					
Thyroid markers[jj]	X	X	X	X	X	-
Ongoing Participant Review						
Concomitant therapy or intervention	X	X	X	X	X	X
Childbearing potential	X	X	X	-	X	X
SAEs/AEs	X	X	X	X	X	X

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CEC = Clinical Event Committee; DP = Disease progression; ECG = electrocardiogram; EOS = end of study; FC = functional class; iMTD = individual maximum tolerated dose; LSV = last study visit; OL = open-label; PAH = pulmonary arterial hypertension; SAE = serious adverse event; TSH = thyroid stimulating hormone; WHO = World Health Organization.

[ii] If participants initiate bosentan rescue treatment under this protocol following PAH disease progression, 4-weekly (±7 days) liver function tests (ALT, AST, alkaline phosphatase, total & direct bilirubin) and hemoglobin (every 4-weeks during the first 4 months of treatment, and quarterly thereafter) need to be performed in addition. Prior to initiation of bosentan treatment, and thereafter every 4 weeks ± 7 days, a negative serum pregnancy test is required in female participants of childbearing potential.

[jj] TSH will be assessed at each time point; thyroid antibodies will be assessed when medically indicated; Free T3 and free T4 will be assessed in case TSH is abnormal or when medically indicated.

2. INTRODUCTION

Selexipag (JNJ-67896049) is an orally available, selective, and long-acting non-prostanoid agonist of the prostacyclin receptor approved and commercially available for the treatment of adult patients with pulmonary arterial hypertension in the United States, the European Union, Japan, and other countries/territories. For the most comprehensive nonclinical and clinical information regarding selexipag, refer to the latest version of the Investigator's Brochure (Selexipag IB). Selexipag was approved in the United States in December 2015 (brand name: UPTRAVI® [Uptravi® USPI]), and in Europe in May 2016 (Uptravi® SmPC).

The term "study intervention/treatment" throughout the protocol, refers to:

- Selexipag or matching placebo (during the double-blind treatment period), and
- Selexipag (during the Open-Label Extension Period).

After a disease progression event, participants who were not treated with an endothelin receptor antagonist (ERA) at baseline and during the study may initiate treatment with an ERA (bosentan, 32 mg dispersible tablets) (refer to Section 10.16). This medication will be provided by the sponsor and is referred to as "bosentan" in this document.

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

2.1. Study Rationale

Pediatric pulmonary arterial hypertension (PAH) is a rare and progressive disorder associated with considerable morbidity and mortality. The current pragmatic treatment algorithm in the pediatric population with idiopathic PAH (iPAH) is predominantly based on expert opinion and includes phosphodiesterase type-5 (PDE-5) inhibitors, ERAs, and inhaled, subcutaneous, and intravenous (iv) prostacyclin pathway agonists (Rosenzweig 2019; Ivy 2013; Galiè 2015). However, the use of targeted PAH therapies in children is almost exclusively based on experience and data from adult studies rather than evidence from clinical trials in pediatric patients. In the absence of randomized controlled clinical trials powered to show the efficacy of those therapies in pediatric patients, the treatment algorithm is based on evidence from adult studies. To date only bosentan is approved in the US and has dosing recommendations in EU for children with PAH, while sildenafil and ambrisentan are approved in EU for treatment of PAH in adolescents and children. No treatment targeting the prostacyclin (PGI2) pathway is approved in children.

Given the significant medical need to develop treatments in children with PAH, further clinical studies in the pediatric population are needed to provide more data for the management of PAH in children.

The rationale for the development of selexipag in children with PAH at this time in the development plan is based on the robust and conclusive results of the pivotal study with selexipag

in adult patients with PAH (GRIPHON/AC-065A302, N=1,156) demonstrating efficacy in delaying disease progression in adults (Sitbon 2015).

In the US, Uptravi is indicated for the treatment of adults with PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. In Europe, Uptravi is indicated for the long-term treatment of PAH in adult patients with WHO functional class (FC) II-III, either as combination therapy in patients insufficiently controlled with an ERA and/or PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

The pediatric development plan of selexipag consists of a Phase 2 study (AC-065A203) to establish the selexipag dose(s) and determine the pharmacokinetics (PK) of selexipag and its active metabolite in children, followed by this current Phase 3 study to assess the efficacy, safety, and tolerability of selexipag in this population based on the dosing recommendation established in AC-065A203.

2.2. Background

Nonclinical Studies

Pharmacologic Profile

While active itself, selexipag is hydrolyzed to an active metabolite ACT-333679 with prolonged terminal half-life and a high selectivity for the prostacyclin receptor. Selexipag and its metabolite possess anti-fibrotic, anti-proliferative, and anti-thrombotic properties. Oral selexipag is effective in an animal model of PAH, improving hemodynamic and structural factors leading to increased survival. Selexipag seems to induce minimal or no tachyphylaxis in rats.

The efficacy of selexipag after oral administration was demonstrated in several nonclinical models of systemic hypertension and pulmonary hypertension (PH). In a rat model of PH, selexipag preserved endothelial function, decreased mean pulmonary arterial pressure (mPAP) and media thickening of pulmonary arteries, and diminished right ventricular wall hypertrophy. Selexipag treatment also led to significant improvement of survival (Selexipag IB).

Unlike PGI2 analogs, selexipag and its active metabolite ACT-333679 bind to the human prostacyclin receptor (IP receptor) with high selectivity over other prostanoid receptors. As shown in cellular assays, IP receptor activation by selexipag or ACT-333679 leads to vascular smooth muscle relaxation, anti-proliferation, and anti-fibrotic effects. Selexipag and ACT-333679 do not activate the molecular processes involved in desensitization of human IP receptors, avoiding receptor internalization and tachyphylaxis (Selexipag IB).

In vitro experiments showed that selexipag and ACT-333679 are highly bound to plasma proteins (>99%) (In vitro study, ACT-293987A and ACT-333679A 2009).

Safety Pharmacology

Safety pharmacology studies revealed effects secondary to expected or exaggerated pharmacology. There was no indication of an effect on ventricular repolarization.

Toxicology

In the repeat-dose toxicity studies in rodents, strong blood pressure (BP) decreases as a result of exaggerated pharmacology induced transient clinical signs, reduced food consumption, and body weight gain. In adult and juvenile dogs, intestine and bone/bone marrow were identified as the main target organs after treatment with selexipag. In dogs less than 1 year old, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. Safety margins for the active metabolite based on the no-observed-effect level for intussusception were 180-fold based on total systemic exposure and when corrected for species differences in receptor potency between human and dog, were 2-fold in relation to human exposure at a dose of 1,600 µg of selexipag twice daily (bid). Intussusception did not occur in mouse or rat toxicity studies. Because of the species-specific propensity of dogs to develop intussusception, this finding is not considered relevant for adult humans. However, as young children are known to be prone to developing intussusception, the use of selexipag in children below 2 years of age is not recommended based on the nonclinical findings.

Increased bone ossification and related changes in the bone marrow in dog studies are considered to be due to the activation of prostaglandin-E2 subtype 4 (EP_4) receptors in dogs. As human EP_4 receptors are not activated by selexipag or its active metabolite, this effect is deemed species-specific and, therefore, not relevant to humans.

Selexipag and its active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.

In the 2-year carcinogenicity studies, selexipag caused an increased incidence of thyroid adenomas in mice and Leydig cell adenomas in rats (Selexipag IB). The mechanisms are rodent-specific. The findings were observed at exposures that were more than 25-fold higher than the exposure in humans and are, therefore, not considered relevant for humans. Tortuosity of retinal arterioles was noted after 2 years of treatment only in rats (Selexipag IB). Mechanistically, the effect is considered to be induced by life-long vasodilation and subsequent changes in ocular hemodynamics. The finding is considered to be species-specific.

Selexipag was not teratogenic in rats and rabbits and had no effect on the fertility of male and female rats. In the rat pre- and postnatal development study, selexipag induced no effects on maternal or pup reproductive function.

Selexipag and its active metabolite were phototoxic in vitro. A dedicated clinical study did not indicate any potential phototoxicity of selexipag in humans (Selexipag IB).

Clinical Studies

Human Pharmacokinetics

Selexipag is rapidly absorbed and is hydrolyzed by carboxylesterase enzymes to its active metabolite, ACT-333679. The PK of selexipag and ACT-333679 were dose-proportional up to a single dose of 800 µg and multiple doses of up to 1,800 µg bid. Steady-state conditions of selexipag and its active metabolite were reached within 3 days. No accumulation in plasma was observed.

Maximum observed plasma concentrations of selexipag and its active metabolite after oral administration are reached within 1 to 3 hours and 3 to 4 hours, respectively. Oxidative metabolism primarily catalyzed by cytochrome P450 (CYP) 2C8 and to a smaller extent by CYP3A4 leads to the formation of hydroxylated and dealkylated products. Uridine 5'-diphosphoglucuronosyltransferase (UGT) 1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceed 3% of the total drug-related material (Selexipag IB). After oral administration, exposure at steady-state to the active metabolite in both healthy subjects and patients with PAH is approximately 3- to 4-fold higher than to the parent compound. In the presence of food, the exposure to selexipag after a single dose of 400 µg was increased by 10% in Caucasian subjects and decreased by 15% in Japanese subjects, whereas exposure to the active metabolite was decreased by 27% (Caucasian subjects) and 12% (Japanese subjects). In the presence of food, the time to reach maximum plasma concentration (t_{max}) of selexipag was delayed by approximately 1 to 1.5 hours. Elimination of selexipag is predominantly via metabolism with a mean terminal half-life of 0.8 to 2.5 hours. The active metabolite has a half-life of 6.2 to 13.5 hours. The total body clearance of selexipag is, on average, 17.93 L/h. Excretion in healthy participants was complete 5 days after administration and occurred primarily via feces (accounting for 93% of the administered dose) compared to 12% in urine. The absolute bioavailability of selexipag is approximately 49%.

No clinically relevant effects of sex, race, disease severity, or body weight on the PK of selexipag and its active metabolite have been observed in adult PAH patients.

The PK characteristics of selexipag and ACT-333679 in the pediatric population was assessed in a Phase 2 study in pediatric patients with PAH (AC-065A203). As in adults, selexipag is uptitrated to the individual maximum tolerated dose (iMTD), assessed based on prostacyclin-related side effects. Selection of the starting dose for pediatric patients is based on their body-weight category, targeting the exposure observed in adult PAH patients at a starting dose of 200 µg, combining data from the population PK model in the GRIPHON study (Modeling and Simulation Report AC-065A302 [GRIPHON], 2014) with pediatric data from the AC-065A203 study.

Efficacy/Safety Studies

In the Phase 1 studies, selexipag was well tolerated after single doses of up to 400 µg (fasted, oral, or iv) and multiple daily oral doses of up to and including 1,600 µg bid (fed). The most frequent adverse events (AEs) were headache, myalgia, arthralgia, jaw pain, nausea, vomiting, diarrhea, and dizziness. No treatment-related effects of selexipag on electrocardiogram (ECG) morphology or cardiac repolarization were noted. There were no clinically relevant changes in vital signs, thyroid markers, or laboratory tests. No changes were observed in the platelet aggregation test, bone turnover, or coagulation markers. In a thorough QT study (AC-065-106) multiple-dose treatment with selexipag (800 µg bid and 1,600 µg bid) did not have any effect on cardiac repolarization in healthy participants. An exploratory Phase 1 study was performed to evaluate the photosensitizing potential of selexipag under steady-state conditions. The study did not indicate that selexipag has clinically relevant photosensitizing potential in humans. More participants reported AEs after administration in the fasted state than in the fed state in the food effect study.

In a study performed in participants with impaired liver function, 1 serious related event of hepatic encephalopathy was reported. No further participants with severe hepatic impairment (Child-Pugh C) were enrolled in the study. In the thorough QT study (AC-065-106), there was 1 serious adverse event (SAE) of symptomatic hypotension reported by a female participant following administration of multiple doses of selexipag (at 1,200 µg dose). This event was severe in intensity and resolved without sequelae on the same day after discontinuation of study treatment.

Study NS-304/-02: This Phase 2a study in patients with PAH enrolled 43 patients who were randomized in a 3:1 ratio to selexipag (n=33) and placebo (n=10). Patients were uptitrated from the starting dose of 200 µg bid to a maximum of 800 µg bid based on the tolerability of each subject. All patients received either an ERA and/or a PDE-5 inhibitor at baseline. After 17 weeks of treatment, a significant 30.3% reduction in pulmonary vascular resistance (PVR) with selexipag compared with placebo was observed (P=0.0045, Wilcoxon rank sum test) and a mean treatment effect on 6-minute walk distance (6MWD) of 24.2 ± 23.7 meters (p=0.2218, Wilcoxon rank sum test) in the Per-Protocol Analysis Set (PPS).

Study AC-065A201: This Phase 2, multicenter, uncontrolled, open-label study in Japan enrolled 37 patients with PAH who received selexipag. Patients were allowed to receive PDE-5 inhibitors and ERAs. Patients were uptitrated from the starting dose of 200 µg bid up to a maximum of 1,600 µg bid based on the tolerability of each subject. The maintenance dose for each patient was determined by Week 12 and maintained up to Week 16. The efficacy evaluation took place at Week 16 of treatment. Long-term treatment continued up to Week 144. Patients could be treated further at the investigator's request. After 16 weeks of treatment, the median change in PVR from baseline -120.9 dyn·sec/cm^5 (95% confidence limits [CLs]): -184.5, -59.5 dyn·sec/cm^5) was observed in the PPS (two-sided p-value of the Wilcoxon signed rank test <0.0001). The geometric mean percentage ratio in PVR (Week 16/baseline×100) was 79.7% (95% CLs: 74.0, 86.0). In a supportive analysis using the all-treated analysis set, similar results to those in the PPS were observed. The long-term treatment phase of the study is currently ongoing.

In the multicenter, double-blind, placebo-controlled, event-driven Phase 3 clinical study GRIPHON (AC-065A302), conducted in 1,156 participants >18 years of age with PAH, selexipag demonstrated a clinically and statistically significant 40% risk reduction compared to placebo in the occurrence of a first morbidity/mortality event up to End of Treatment (EOT) +7 days (hazard ratio [HR] for selexipag versus placebo: 0.60; 99% confidence interval [CI]: 0.46-0.78; 1-sided unstratified log-rank P <0.0001). Results of all supportive analyses on the primary endpoint were consistent with that of the main analysis, and the observed treatment effect was also consistent across subgroups (PAH etiology, region, ethnicity, gender, age, WHO FC, baseline PAH background medication) (Sitbon 2015; Selexipag IB).

The secondary endpoints of change from baseline to Week 26 in 6MWD measured at trough and time to first PAH-related death or hospitalization due to PAH showed a statistically significant effect favoring selexipag over placebo. The secondary endpoints of absence of worsening in WHO FC from baseline to Week 26 and of time to death (all causes) up to study closure did not show a difference between selexipag and placebo (Selexipag IB).

In the GRIPHON study, patients were treated for up to 4.2 years. The most frequent adverse drug reactions observed with selexipag were related to its mode of action and were of the same type as those seen with other IP receptor agonists, ie, prostacyclin analogs. These included: headache (65% vs 32% in placebo group), diarrhea (42% vs 18%), nausea (33% vs 18%), jaw pain (26% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), and myalgia (16% vs 6%). A total of 43.8% and 47.1% of patients in the selexipag and placebo groups, respectively, had at least 1 SAE. The majority of SAEs were consistent with the underlying PAH condition. PAH worsening and right ventricular failure were the most frequently reported SAEs, and both were reported at lower frequencies in the selexipag group (14.4% and 5.9%, respectively) than in the placebo group (22.0% and 7.1%, respectively). A total of 31.7% of patients in the selexipag group and 37.1% in the placebo group had at least 1 AE leading to discontinuation of study treatment. Other than prostacyclin-associated AEs, most of the AEs that led to discontinuation of study treatment were SAEs associated with the underlying PAH disease.

Overall, in the GRIPHON study, the nature and incidence of typical prostacyclin-associated AEs (ie, headache, flushing, diarrhea, nausea, vomiting, jaw pain, myalgia, and arthralgia) on selexipag was largely in line with that observed with prostacyclin and prostacyclin analogs (Sitbon 2015; Selexipag IB).

Hypotension was reported more frequently in the selexipag group than in the placebo group (5.9% and 3.8%, respectively). In the selexipag group 9.7% of patients had systolic blood pressure (SBP) <90 mmHg on at least 1 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.

In the GRIPHON study, a transient increase in mean heart rate of 3 to 4 beats per minute at 2 to 4 hours post dose was observed. ECG investigations showed sinus tachycardia in 11.3% of patients in the selexipag group compared to 8.8% in the placebo group.

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 than in the placebo group. The corresponding laboratory changes were small reductions in thyroid stimulating hormone(TSH) at most post-baseline visits. A possible association between thyroid disorders and PAH is described in the literature (Marvisi 2013). Previously published investigations showed that prostaglandins may influence thyroid function by a direct effect on specific prostaglandin membrane receptors (Chadha 2009).

Other AEs included nasopharyngitis (very common); decreased appetite, weight decreased, nasal congestion, rash, urticaria, erythema, abdominal pain, and pain (all reported as common).

Importantly, there were no additional safety and tolerability findings in the GRIPHON study in those patients receiving selexipag concomitantly with both an ERA and a PDE-5 inhibitor.

For efficacy data from other completed or ongoing selexipag clinical studies in adult patients with PAH, chronic thromboembolic pulmonary hypertension (CTEPH), Raynaud's Phenomenon secondary to systemic sclerosis (SSc) and arteriosclerosis obliterans-intermittent claudication (ASO-IC), refer to the Investigator's Brochure (Selexipag IB). Safety data from other completed or ongoing selexipag clinical studies in adult patients with PAH, CTEPH, Raynaud's Phenomenon secondary to SSc, and ASO-IC show a safety profile consistent with that seen in the GRIPHON study (Selexipag IB).

2.3. Benefit/Risk Assessment

Risks for Study Participation

The potential risks of participation in the study include exposure to study intervention with the potential for side effects, and the inherent risks associated with venipuncture and blood sample collections. The study has been designed to minimize these inherent risk factors by keeping blood sampling procedures to a minimum and including efficacy assessments that are non-invasive.

Benefits for Study Participation

Uptravi (selexipag) is a selective IP receptor agonist for oral use with PK characteristics suitable for bid dosing and with proven efficacy and safety in adults with PAH. The efficacy of selexipag in the treatment of adult patients with symptomatic PAH was demonstrated in GRIPHON, a large (N=1,156) long-term (mean duration 1.5 years and up to 4.2 years), controlled outcome study. The treatment effect was consistent across WHO 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 2 such medicines (30% of the study population). The known similarities between PAH disease in adult and pediatric patients suggest that pediatric PAH patients could benefit from selexipag treatment, and the tolerability and safety profile of selexipag administered to children is expected to be consistent with that of adult patients.

Benefit Risk Assessment for Study Participation

The benefit of medicines acting on the prostacyclin pathway (IP receptor agonists) in the treatment of PAH in adults is established, as acknowledged by current treatment guidelines (Galiè 2015, Humbert 2022). To date, selexipag is the only orally available IP receptor agonist approved globally for long-term treatment across WHO FC II-III, primarily in combination with current first-line oral PAH-specific medicines, in adult patients in need of additional therapy because of insufficient disease control. Uptravi represents an important additional treatment option for these patients.

Currently, no medicines targeting the prostacyclin pathway are approved for pediatric use in PAH. An effective and orally available therapy acting on the prostacyclin receptor such as selexipag introduced at medically appropriate stage of PAH disease (WHO FC II-III), and primarily in combination with current first-line oral PAH-specific medicines in patients in need of additional

therapy because of insufficient disease control would represents a major advance to the therapeutic management of PAH pediatric patients. Selexipag is not indicated or foreseen for use as an alternative to iv prostacyclin analogs (epoprostenol, treprostinil) in patients with the most severe PAH (WHO FC IV). Consequently, selexipag will not be compared to an active control affecting the prostacyclin pathway, but instead will be compared to matching placebo. The use of placebo is ethically acceptable in this study as it will be added to standard of care which can include PDE-5 inhibitor and/or ERA treatment and thus follows PAH treatment guidelines (Ivy 2013; Rosenzweig 2019).

The following measures will be taken to minimize the potential risks for the pediatric participants participating in this study:

- Enrollment will start with study participants in age cohorts 1 (≥12 to <18 years of age) and 2 (≥6 to <12 years of age), ie, those age groups for whom the dosing was confirmed in the pediatric Phase 2 study AC-065A203 (refer to PK Interim Analysis Report-1 AC-065A203 2019 and PK Interim Analysis Report-2 AC-065A203 2020). Enrollment into age cohort 3 (≥2 to <6 years of age) will be initiated after the starting dose and uptitration regimen are confirmed in the corresponding age cohort of AC-065A203 (PK Final Analysis Report AC-065A203 2022). Results of the dosing confirmation are documented in interim and final pharmacokinetic analysis reports. If the dosing has to be adjusted based on emerging data for age cohort 3, the protocol will be amended accordingly.
- At randomization, participants will be receiving at least 1 PAH-specific therapy available in the respective participating countries/territories, which may include an ERA and/or PDE-5 inhibitors/soluble guanylate cyclase stimulator. In case a participant was not treated with an ERA at randomization, bosentan will be offered as rescue therapy when a participant experiences a PAH worsening event, thus ensuring access to an age-appropriate PAH-treatment, which is approved for treatment of children with PAH in many countries/territories. For information regarding bosentan refer to the bosentan Investigator's Brochure (Bosentan IB).
- Inclusion and exclusion criteria are carefully designed in this protocol (refer to Sections 5.1 and 5.2) and are aligned with discussion of the pediatric PAH development program with Health Authorities (EMA/FDA). A Baseline Characteristics Adjudication Committee (BCAC) will be used to support determination of eligibility of participants by centrally reviewing participants with coincidental congenital heart disease before their randomization (refer to Section 10.4).
- The doses selected for this study are based on a population PK model developed using data from the GRIPHON (Modeling and Simulation Report pediatric dose selection, 2016) study combined with data from the PK study AC-065A203 conducted in the pediatric population from ≥2 to <18 years of age.
- The starting dose (and the corresponding dose increases used in the uptitration phase) will be based on body weight and determined by the population PK model developed using data from the GRIPHON study (Modeling and Simulation Report AC-065A302 [GRIPHON] 2014) and confirmed by pediatric PK data acquired from AC-065A203 (Clinical Study Protocol AC-065A203 Version 2 2018). The starting dose levels in the pediatric population are designed to target the combined exposure (ie, the area under the plasma concentration versus

time data, $AUC_{\tau,ss,combined}$, to both parent drug and active metabolite, ACT-333679, corrected for their relative potencies) observed in adult subjects with PAH at the clinical starting dose of 200 µg (Modeling and Simulation Report AC-065A302 [GRIPHON], 2014). Specific recommendations are made for study drug interruption and/or permanent discontinuation (refer to Section 7.1).

- The study does not mandate hemodynamic assessments by right heart catheterization (RHC) which are considered invasive and may pose a risk in children. Historical RHC results are used to confirm eligibility. RHC assessments during the study will only be recorded if performed as per local standard of care.
- Close monitoring during the initial uptitration period up to Week 12 includes weekly phone calls or site visits, followed by 12-weekly contacts (phone calls and site visits alternating every 3 months) for the entire study duration will allow for early detection and management of AEs.
- Specific recommendations are made regarding the management of AEs associated with tolerability during the initial uptitration phase along with the recommendation that patients take study drug in the evening and with food to improve tolerability (refer to Section 6.1). Guidance will be provided to the investigator and parents/participants in case of clinical signs compatible with gastrointestinal ileus or obstruction and hyperthyroidism (refer to Sections 2.2 and 7.1). Participants' growth and development will be monitored throughout their study participation (refer to Sections 8.3.1 and 8.3.4). Safety surveillance for participants in this study will additionally be ensured by an IDMC, which will periodically review available safety data (refer to Section 9.8).
- Participants will receive additional care as a result of participating in a clinical trial including close monitoring at an expert PAH-center. The investigator will monitor the benefit-risk ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual participant level. The investigator may discontinue study treatment or study procedures if, on balance, he or she determines that continuation would be detrimental to the participants' wellbeing.
- At the time of PAH disease progression and in countries/territories with access to PAH specific therapies targeting the prostacyclin pathway, participants can stop double-blind treatment, and receive those treatments if considered to be in their best interest. If a positive benefit risk for treating children with PAH with selexipag is established at the time of the Analysis 2 treatment with selexipag will be offered to all participants in the open-label extension period (OLEP; except those who stopped double-blind study medication selexipag/placebo prematurely).

Selexipag is not indicated or foreseen for use as an alternative to iv prostacyclin analogs (epoprostenol, treprostinil) in patients with severe PAH (WHO FC IV), and therefore such participants are excluded.

Based on the measures taken in this study to minimize the risks to pediatric patients, the potential benefits of study participation outweigh the associated risks.

More detailed information about the known and expected benefits and risks of selexipag are provided in the Investigator's Brochure (Selexipag IB).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate whether the addition of selexipag to Standard of Care treatment delays disease progression in children with PAH in comparison to placebo.	• Time to disease progression from randomization up to 7 days after study treatment discontinuation. Disease progression will be adjudicated by a blinded CEC and is defined as the first occurrence of either of the following components: – Death (all causes) – Atrial septostomy or Potts' anastomosis, or registration on lung transplant list – Hospitalization due to worsening PAH[a] – Clinical worsening of PAH defined as: Need for, or initiation of new PAH-specific therapy[b] or iv diuretics or continuous oxygen use AND at least one of the following: o Worsening in WHO FC, or o New occurrence or worsening of syncope (in frequency or severity as per medical judgment), or o New occurrence or worsening of at least two PAH symptoms, ie, shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue), or o New occurrence or worsening of signs of right heart failure not responding to oral diuretics. Investigators will document the condition of the participant at baseline (narrative and echocardiography). In the presence of disease progression, the investigator will prepare a narrative of the participant's condition, perform an echocardiography, and test the level of NTproBNP to document disease progression. These data, together with relevant electronic Case Report Form (eCRF) data and any other relevant supportive routine assessment (eg, RHC, magnetic resonance imaging, uric acid, etc) and potential hospital discharge summary (if applicable), will be provided to the CEC for adjudication. Data on AEs specific to

a Excluding hospitalizations that are elective, routine, or clearly attributable to the appearance/worsening of comorbidities (eg, pneumonia).

b eg, ERA, PDE-5 inhibitor, prostanoids, soluble guanylate cyclase stimulator.

Objectives	Endpoints
	prostanoids (eg, jaw pain) will not be provided to the CEC to keep them blinded. The CEC will determine the components of the event, the relationship of hospitalization with PAH, and the event onset date. If there is a missing assessment (eg, no WHO FC), the CEC will ultimately be responsible for qualifying or disqualifying the event and the date of the event for the analysis of the primary endpoint, using all available clinical data.
Secondary	
• To evaluate whether the addition of selexipag to Standard of Care treatment decreases NT-proBNP in children with pulmonary arterial hypertension in comparison to placebo.	• Change in $\log_2$(NT-proBNP) from baseline to Week 24 ($\log_2$(Week 24/Baseline)).
• To assess the safety and tolerability of selexipag in children with PAH.	• Treatment-emergent AEs and serious AEs. • AEs leading to premature discontinuation of study treatment. • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points. • Growth: Change in body weight and height from baseline to all assessed time points. • Sexual maturation (Tanner stage) change from baseline to all assessed time points up to 3 days after study treatment discontinuation. • Treatment-emergent electrocardiogram abnormalities. • Treatment-emergent marked laboratory abnormalities at each time point of assessment. • Treatment-emergent change from baseline in thyroid stimulating hormone over time. • Treatment-emergent change in selected laboratory variables from baseline to all assessed time points. A treatment-emergent event or abnormality is temporally associated with the use of study treatment whether or not considered by the investigator as related to study treatment.

Objectives	Endpoints
• To evaluate whether selexipag can delay hospitalization and death due to PAH worsening in children.	• Time to first CEC-confirmed hospitalization or death for PAH occurring from Randomization until 7 days after study treatment discontinuation. The CEC will determine the relationship of death and hospitalization with PAH and the event onset date.
• To assess the trough plasma concentrations of selexipag and its active metabolite at steady state in children with PAH.	• Trough plasma concentration at steady-state ($C_{trough,ss}$) of selexipag and its metabolite ACT-333679 collected during the maintenance period.
Exploratory	
• To explore the following safety and efficacy variables.	• Time to death (all causes) occurring between Randomization and the Analysis Visit for each Analysis. • Time to first CEC-confirmed hospitalization for PAH occurring between randomization and until 7 days after study treatment discontinuation. • Time to first CEC-confirmed death due to PAH occurring from randomization until 7 days after study treatment discontinuation. • Time to CEC-confirmed disease progression up to the Analysis Visit for each Analysis. • WHO FC III/IV (yes/no) at each time point of assessment up to 7 days after study treatment discontinuation. • Change in WHO FC from baseline/enrollment to each time point of assessment up to 7 days after study treatment discontinuation. • Change from baseline to each time point of assessment in exercise capacity up to 7 days after study treatment discontinuation as measured by the 6-minute walk distance in children ≥6 years of age who are developmentally able to understand and perform the test. • Change in physical activity (measured by accelerometry) from baseline to 1 year (48 weeks) after Randomization. • Change in Panama FC from baseline to each time point of assessment up to 7 days after study treatment discontinuation. • Percent of baseline in serum NT-proBNP at each time point of assessment up to 7 days after study treatment discontinuation.

Objectives	Endpoints
	• Change from baseline in echocardiographic variables (imaging and Doppler evaluation) such as right ventricular systolic pressure, tricuspid annular plane systolic excursion, etc, at each time point of assessment up to 7 days after study treatment discontinuation. • Time to clinical worsening from randomization up to 7 days after study treatment discontinuation, where clinical worsening is defined as at least one of the following components (adapted from the CHMP definition [EMEA 2008]): 1. All-cause death. 2. Non-planned PAH-related hospitalization. 3. PAH-related deterioration identified by at least one of the following parameters: i. increase in WHO FC; ii. deterioration in exercise testing (15% decrease from baseline in 6MWD) iii. new or worsening signs or symptoms of right-side heart failure.
• To explore the Quality of Life (QoL).	In a subset of countries/territories, change from baseline to all time points of assessments in: • QoL as measured by the PedsQL™ 4.0 Generic Core Scales Short Form. • QoL as measured by the disease-specific PedsQL™ 3.0 Cardiac Module using the "heart problems and treatment" component only. • QoL as measured by the PedsQL™ Multidimensional Fatigue Scale standard version using the "general fatigue" component only. Each of these endpoints will be analyzed as assessed by participants and as assessed by a caregiver (eg, parent/LAR). Questionnaires are adapted for following age categories: • Toddlers: 2 to 4 years of age • Young children: 5 to 7 years of age • Children: 8 to 12 years of age • Adolescents: 13 to 18 years of age For the youngest age category (toddlers) the questionnaire exists only for parent(s)/LAR(s), ie, Parent report). Young children will be interviewed by a site staff member. For the

Objectives	Endpoints
	two oldest age categories, separate questionnaires exist for parent(s)/LAR(s) and for participants (ie, Child report) and address the same items.
• Other.	• Palatability of the study intervention at Week 4, Week 12, and EOT, assessed using a 5-point facial hedonic scale. • Acceptability of the study intervention at Week 4, Week 12, and EOT, as assessed through a 3-point categorical scale as to whether the child swallowed the medication.
Exploratory – Open-Label Period	
• To explore the long-term safety, tolerability, and efficacy of selexipag in children with PAH.	**Tolerability/Safety** • Treatment-emergent AEs and serious AEs. • AEs leading to discontinuation of study treatment. • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed time points. • Growth: Change in body weight and height from baseline to all assessed time points up. • Sexual maturation (Tanner stage) change from baseline to all assessed time points up to 3 days after study treatment discontinuation. • Treatment-emergent electrocardiogram abnormalities. • Treatment-emergent marked laboratory abnormalities at each time point of assessment. • Treatment-emergent change from baseline in thyroid stimulating hormone over time. • Treatment-emergent change in selected laboratory variables from baseline to all assessed time points. A treatment-emergent event or abnormality is temporally associated with the use of study treatment whether or not considered by the investigator as related to study treatment. **Efficacy** • Change in modified New York Heart Association/WHO FC from the date of first dose in the OLEP to each time point of assessment up to 7 days after study treatment discontinuation.

Objectives	Endpoints
	• Change in Panama FC from the date of first dose in the OLEP to each time point of assessment up to 7 days after study treatment discontinuation. • Time to (investigator assessed) disease progression from the date of first dose in the OLEP up to 7 days after study treatment discontinuation.

HYPOTHESIS

The primary hypothesis of this study is that selexipag reduces the risk of disease progression (measured as time from randomization to first CEC-confirmed disease progression event) compared to placebo, in pediatric participants with PAH.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group, study with OLEP to assess the efficacy and safety of selexipag as add-on to standard of care in children aged ≥2 to <18 years with PAH (WHO Group 1).

Enrollment will occur according to the following age cohorts:

- Cohort 1: ≥12 to <18 years of age.
- Cohort 2: ≥6 to <12 years.
- Cohort 3: ≥2 to <6 years.

Enrollment will start with study participants in age cohorts 1 (≥12 to <18 years of age) and 2 (≥6 to <12 years of age), ie, those age groups for whom the dosing was confirmed in the pediatric Phase 2 study AC-065A203 (PK Interim Analysis Report-1 AC-065A203 2019 and PK Interim Analysis Report-2 AC-065A203 2020). Enrollment into age cohort 3 (≥2 to <6 years of age) will be initiated after the starting dose and uptitration regimen are confirmed in the corresponding age cohort of AC-065A203 (PK Final Analysis Report AC-065A203 2022). Results of the dosing confirmation are documented in interim and final pharmacokinetic analysis reports. If the dosing has to be adjusted based on emerging data for age cohort 3, the protocol will be amended accordingly.

Approximately 125 participants are expected to be randomized in the double-blind treatment period. Within the study, 4 analysis timepoints are planned CCI [redacted]

- Analysis 1 CCI [redacted] will be performed with a data cutoff date when at least 80 participants have been treated and followed up for at least 24 weeks in the double-blind treatment period. Analysis 1 will be performed and reported by a separate unblinded CCI [redacted] team. The study team remains blinded to this analysis.

- Analysis 2 CCI [redacted] will be performed with a data cutoff date when approximately 125 participants have been followed up for at least 24 weeks or prematurely discontinued the study in the double-blind treatment period. The study team will be unblinded after database lock for Analysis 2. Site personnel and participants will remain blinded until the announcement of the end of the double-blind treatment period.
- Analysis 3 is CCI [redacted] at the end of the double-blind treatment period after all participants included in Analysis 2 have completed their EOT visit. Site personnel and participants will be unblinded.
- Analysis 4 is the analysis of the OLEP after all participants have completed the 3-year OLEP or have prematurely discontinued the study.

After the double-blind treatment period, an OLEP will start and continue for 3 years if the results of Analysis 2 support positive benefit/risk ratio in children.

Participants will be centrally randomized via an interactive web response system (IWRS) in a 1:1 ratio to either selexipag or placebo. Treatment allocation will be stratified by WHO FC (II vs III), and for presence of background PAH-specific treatment (monotherapy vs combination therapy) at baseline.

The study starts with the first Informed Consent Form (ICF) signed by the first participant and ends with the last safety follow-up telephone call or visit of the last participant.

The study consists of the following consecutive periods and milestones:

- **Screening Period:** Starts with the signature of the informed consent form and ends with the participant's randomization or confirmation of screening failure.
- **Double-blind Treatment Period:** Starts from randomization and ends on the day of the last dose of double-blind study intervention. It includes:
  - **Uptitration Period:** Starts from the first dose of study intervention until the participant reaches the iMTD. This period is estimated to last up to 12 weeks.
  - **Maintenance Period:** Starts after the uptitration period and ends with last dose of double-blind study intervention. Participants will continue study intervention at a stable dose from reaching iMTD until Week 16. After Week 16, participants who did not achieve the maximum allowed dose of their respective weight category may be further uptitrated if it is considered in the best interest of the participant per the investigator's judgment. The dose may be downtitrated at any time if deemed appropriate by the investigator.

  The duration of the double-blind treatment period will be different for individual participants and will depend on the time of entering the study and will last until all participants included in Analysis 2 have completed their EOT visit. Participants may discontinue double-blind treatment early (eg, due to an AE or initiation of parenteral or inhaled prostacyclin treatment).

- **Post Treatment Observation Period**: Participants who prematurely discontinue the double-blind treatment period will enter a Post Treatment Observation Period. This period starts from the EOT visit and ends with the announcement of end of double-blind treatment period.
- **Post Event Treatment Period:** Starts after the CEC confirms disease progression and lasts until the announced end of double-blind treatment period. Participants will remain on double-blind study intervention and treatment with bosentan (bosentan, 32 mg dispersible tablets) will be offered by the sponsor if deemed beneficial and requested by the investigator to participants who were not treated with an ERA at baseline and during the study (refer to Section 10.16). Participants who initiate parenteral or inhaled prostacyclin treatment must discontinue double-blind study intervention and enter the Post Treatment Observation Period.
- **EOT Visit:** Upon the announcement of end of double-blind treatment period, the EOT visit will be scheduled. In case of premature treatment discontinuation, this visit will be conducted within 10 days of the last dose of double-blind study intervention.
- **Analysis Visits during the Double-blind Treatment Period:** Analyses 1, 2, and 3 refer to Section 9.2) will be announced by the sponsor. Analysis Visits for all participants will be scheduled within 6 weeks of the announcement for each analysis. Data collected during these visits will be included in the respective analyses. Analysis 1 will be performed by an unblinded CCI team, independent from the study conduct, CCI The sponsor will announce the closure of enrollment and the end of the double-blind treatment period as applicable.
- **OLEP:** Starts from the first dose of open-label selexipag treatment and ends with the End of Study (EOS) visit. During the OLEP, open-label selexipag treatment will be offered if the results of Analysis 2 confirm a positive benefit/risk ratio of selexipag for children with PAH. Participants who do not plan to enter the OLEP, will stop double-blind treatment and have a

safety follow-up call 30 days later (refer to Safety Follow-up Period) which will be their EOS contact. Treatment assignment during the double-blind treatment period will be unblinded via IWRS: Participants on selexipag during the double-blind treatment period will continue treatment at their iMTD during the OLEP, for those previously on placebo, the iMTD will need to be identified via uptitration as described in Section 6.1.

At the last study visit (LSV), participants who complete the OLEP and would benefit from continued selexipag treatment will either be switched to commercial Uptravi (applicable to participants who live in a country/territory where selexipag is commercially available and approved for the treatment of pediatric participants with PAH), or, if eligible, will be offered to participate in a PTA program or a subsequent open-label study (see Section 6.8).

- **Safety Follow-up Period:** Starts on the day after the last dose of study intervention (after either the double-blind or the open-label study intervention) and ends 30 days thereafter with a safety telephone call. Participants who do not plan to enter the OLEP will have this Safety Follow-up Period 30 days after the Analysis Visit for each Analysis. In the OLEP this call constitutes the **EOS contact**. For participants who complete the OLEP and who are eligible for a PTA or the subsequent open-label study (see Section 6.8), the safety follow-up period will be waived and the EOS call is defined as the LSV in the Open-Label Extension Period.

An IDMC will be commissioned for this study. Refer to Committees Structure in Section 10.4, Regulatory, Ethical, and Study Oversight Considerations for details.

To preserve the study blind up to the database lock of Analysis 2, a blinded study team will be responsible for study conduct and oversight.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Study design

As per ICH (ICH E11 Guidelines) the efficacy of medications approved in adults can be assumed to be comparable for the same indication in children if the disease process is similar in the 2 populations, which is the case for PAH (Barst 2011). Beyond the neonatal period, the pathology of pulmonary vascular disease is the same across age ranges. The IP receptors histologically appear to be similar in children and adults and the histopathological findings seen in adults with PAH are also observed in children with PAH. Both populations have vascular and endothelial dysfunction and present at diagnosis with elevations in PVR and pulmonary arterial pressure (Barst 2011). The data on prostacyclins and prostacyclin analogs show the same effect in adults and children (Barst 2011). Therefore, similar efficacy and tolerability as observed in adults (GRIPHON) is anticipated in children.

Medications acting on the prostacyclin pathway (IP receptor agonists) are of established benefit in the treatment of PAH, as acknowledged by current treatment guidelines (Rosenzweig 2019; Galiè 2015; Humbert 2022). However, none of these medications have been approved for children; instead, inhaled, subcutaneous and iv prostacyclin or its analogues are being utilized off--label (Galiè 2015; Ivy 2013). To date, only 3 PAH-targeted drugs have been approved for use in pediatric PAH: bosentan, an ERA (approved by both the EMA and FDA), and sildenafil, a PDE-5

inhibitor, and ambrisentan (approved by the EMA). Additional PAH medications are frequently used in children with iPAH/heritable PAH and pulmonary arterial hypertension associated with congenital heart disease (aPAH-CHD). These compounds (eg, macitentan, tadalafil, riociguat, as well as selexipag) are however considered experimental pediatric PH pharmacotherapy until prospective clinical data become available (Hansmann 2016).

A long-term, double-blind controlled study investigating time to disease progression is thus appropriate to provide relevant efficacy, safety, and PK data.

Stratification

WHO FC III is associated with a higher risk of death and/or disease progression (Galiè 2015). Differences in survival have been reported in patients on combination therapy compared to monotherapy (Zijlstra 2014). Participants will therefore be stratified for these prognostic factors (refer to Section 6.3).

Study population

Pediatric participants with PAH from ≥2 to <18 years of age and of all etiologies relevant in children with PAH are enrolled to cover a generalizable pediatric PAH population. Within the subgroup of aPAH-CHD, the protocol excludes children with Eisenmenger syndrome, as well as children with open and non-coincidental left-to-right shunts, due to a lack of adult data in these indications.

Children with PAH under 2 years of age are not part of the study population due to potentially increased risk of intestinal intussusception, based on toxicological findings of intestinal intussusception in young dogs treated with selexipag and the high background incidence of intussusception in infants (Newman 1987; Hutchison 1980; Pollack 1991; Waseem 2008; Stringer 1992).

Primary endpoint

Recent guidelines for pediatric PAH patients acknowledge the suitability of clinical worsening as an endpoint in pediatric trials (Rosenzweig 2019). Morbidity and mortality are considered as the most clinically meaningful outcomes in PAH (Ivy 2013; Chakinala 2013). Successful use of such endpoints in adult studies ((Pulido 2013; Sitbon 2015) suggests that it is suitable to also consider similar endpoints and assessments in the pediatric population. The proposed composite primary endpoint in this study is based on the one used in the pivotal adult selexipag PAH study (GRIPHON [Clinical Study Report AC-065A302 (GRIPHON) 2014]) and was modified to account for children-specific requirements or limitations. All morbidity components of this composite endpoint are considered clinically meaningful, denoting disease progression. As in adults, clinical evidence of right ventricular failure, progression of symptoms, and advanced WHO FC are recognized to be associated with a higher risk of death in pediatric PAH patients and were built into the component of PAH worsening (Chin 2005; Sitbon 2002; Ivy 2010; Moledina 2010; van Loon 2010; Ivy 2013). A retrospective cohort analysis also supports the use of clinical worsening as a composite study endpoint in children with PAH (Ploegstra 2015a). A morbidity-

and mortality-based primary endpoint is also being used in the macitentan development program in children with PAH (Study Protocol Version 3, TOMORROW 2018).

Secondary and exploratory endpoints

Currently, no surrogate biomarker for PAH in children has been formally validated. Nevertheless, NT-proBNP as a marker for myocardial strain / pressure overload has been widely used in the risk-stratification and monitoring of disease progression and treatment success in pulmonary hypertension in adults (Benza 2019) and pediatrics (Ploegstra 2015b).

Pro-brain natriuretic peptide is split by the protease furin into inert N-terminal proBNP (76 amino acids) and physiologically active BNP (32 amino acids) (Semenov 2016). BNP is released by cardiomyocytes in response to cardiac volume- and pressure-overload. The physiological functions of BNP include diuresis, vasodilation, inhibition of renin and aldosterone production and cardiac and vascular myocyte growth (Hall 2004). The physiological net-effect of BNP is to reduce pre- and post-load through relaxation of smooth muscle cells and movement of fluid into the interstitial space (Maries 2013). The main driver of elevated proBNP plasma concentrations is heart failure. Similarly, NT-proBNP levels are indicators of ventricular strain and related to the degree of RV dysfunction (Takatsuki 2012).

In healthy individuals, plasma BNP concentrations are very low (1 fmol/mL), but in response to congestive heart failure, circulating concentrations of BNP are dramatically elevated (Maries 2013).

The half-life of NT-proBNP is longer compared to BNP (90 minutes versus 20 min [Di Angelantonio 2009]). In addition, unlike BNP assays, many NT-proBNP assays use the same antibodies, so results from different manufacturers show greater agreement (Semenov 2016, Chami 2022). Therefore, overall, NT-proBNP rather than BNP is usually utilized as an indicator of right, left or congestive heart failure.

N-terminal pro-brain natriuretic peptide levels are confounded by BMI, renal function, sepsis, metabolic syndrome as well as age and gender (Sedaghat 2019).

In PAH, as in other forms of PH, increased myocardial stress and right ventricular hypertrophy due to an increase in PVR and pulmonary arterial pressure might cause a rise in (NT-pro) BNP.

Physical daily activity assessed by accelerometry has been shown to correlate with 6MWD in adult PAH patients and is significantly lower in patients with WHO FC III/IV as compared to WHO FC I/II. Furthermore, PAH patients with daytime activity <15 hour/day had shorter transplant-free survival (Kaplan-Meier [KM] estimate) as compared to patients with longer daytime activity. Thus, physical activity measured by accelerometry may be used as a tool to assess functional capacity, disease severity and prognosis in patients with PH (Pugh 2012; Ulrich 2013). Accelerometry is being used in children excluding infants for indications other than PAH (Cliff 2009; Robertson 2011; Van Cauwenberghe 2001). Only limited data exist in children with PAH (Zijlstra 2017) and thus change in physical activity will be assessed as an exploratory endpoint in this study.

WHO FC, echocardiographic variables of right ventricular size and function (such as right ventricular systolic pressure, tricuspid annular plane systolic excursion, left ventricular eccentricity index), serum NT-proBNP and are amongst the recognized indicators for risk in pediatric patients with PAH (Rosenzweig 2019) and will therefore be included as exploratory assessments in this study.

Because the 6-minute walk test (6MWT) cannot reliably be assessed in children with PAH (Adatia 2013) across all age ranges, it will only be assessed in children ≥6 years in an exploratory manner.

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups.

Treatment with bosentan after PAH progression

Participants are treated with study intervention (selexipag/placebo) in addition to standard-of-care treatment, which may include PDE-5 inhibitors and endothelin receptor antagonists. At least 1 such PAH-specific treatment must be present at baseline. For participants not treated with an ERA at randomization and during the study, treatment with bosentan will be offered by the sponsor following PAH-progression (refer to Section 10.16). Escalation of treatment upon PAH disease progression is in line with treatment guidelines for patients with PAH (Galiè 2015). Offering the dispersible formulation of bosentan after PAH-progression as rescue treatment therefore is an option corresponding to the standard of care in many countries/territories.

OLEP

The OLEP will only be initiated after a positive benefit-risk ratio of treatment with selexipag in children with PAH has been established at Analysis 2 (refer to Section 9.2) and after treatment allocation during double-blind study is unblinded. Participants on selexipag during the double-blind treatment period will continue treatment at their iMTD during the OLEP, for those previously on placebo, the iMTD will need to be identified via uptitration as described in Section 6.1.

4.2.1. Study-Specific Ethical Design Considerations

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

to understand the risks, benefits, and potential AEs of the study and provide their consent/assent voluntarily will be enrolled.

The primary ethical concern is the use of placebo as a comparator. In the setting of this study, the use of placebo is considered acceptable because the inclusion criteria require the presence of at least 1 allowed PAH-related concomitant therapy (PDE-5 inhibitor, and/or ERA) (refer to Section 2.3). In addition, the study provides rescue study medication bosentan to patient not treated with ERA at baseline with PAH disease progression event.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies and/or local regulations. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refer to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

The total blood volume to be collected (approximately 4.8 mL per visit, refer to Section 8) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the Bulletin of the World Health Organization (WHO Bulletin 2011). The recommended blood sampling volumes associated with minimal risk to children range from 1 to 5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks.

4.3. Justification for Dose

The starting dose and uptitration scheme for pediatric patients is based on their body-weight category (refer to Section 6.1). Combining the population PK model developed based on the GRIPHON study with pediatric PK data from the AC-065A203 study, the pediatric dosing recommendations have been developed to target the exposure observed in adult PAH patients within the dose range from 200 to 1,600 µg bid, which is the dose range approved for adult PAH patients (Uptravi® SmPC, Uptravi® USPI). A continuous relationship between dose and body weight was used to define body-weight categories and starting dose for each body-weight category such that – on average – the exposure ($AUC_{\tau,ss,\ combined}$) will be comparable to that of a 70 kg adult but not exceeding the exposure of a 50 kg adult.

The exposure is defined as the combined exposure to selexipag and ACT-333679 corrected for potency ($AUC_{\tau,ss,\ combined}$). It is derived as:

$AUC_{\tau,ss,\ combined} = 1/38 * AUC_{\tau,ss,\ selexipag} + 37/38 * AUC_{\tau,ss\ ACT\text{-}333679.}$

The potency of ACT-333679 was estimated to be 37 times that of selexipag. ACT-333679 is, therefore, the major contributor to the efficacy of selexipag (Research Report 2014).

Enrolment into this study will not be initiated before the dosing have been confirmed by the relevant age cohort in the AC-065A203 study (Clinical Study Protocol AC-065A203, Version 3 2019).

As in adults, selexipag will be uptitrated to the individual maximum tolerated dose (iMTD). Tolerability will be assessed based on prostacyclin-related side effects. Therefore, in the absence of major PK differences between adults and pediatrics, applying an equivalent dose uptitration regimen in children should lead to exposures in pediatric participants similar to those in adults and should also result in consistent efficacy results and safety profiles.

4.4. End of Study Definition

A participant will be considered to have completed the double-blind treatment period if he or she has completed all assessments until the announced end of double-blind treatment period. After the double-blind treatment period is completed and a positive benefit-risk ratio of selexipag has been confirmed in children with PAH, participants will be offered to enter the Open-label Extension Period. The end of study coincides with the EOS visit of the Open-label Extension Period for these participants.

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

5. STUDY POPULATION

Screening for eligible participants will be performed within 42 days before administration of the study intervention. Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any screening procedures is allowed.

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

5.1. Inclusion Criteria

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

1. Parent(s) (preferably both, if available, or as per local requirements, or their legally authorized representatives [LARs]) must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Informed Consent Process in Section 10.4, Regulatory, Ethical, and Study Oversight Considerations.

2. Male and female participants between ≥2 and <18 years of age weighing ≥9 kg at Randomization.

3. PAH diagnosis confirmed by documented historical RHC performed at any time before participant's screening, and characterized by:

   - mPAP ≥25 mmHg,

   AND

   - Pulmonary arterial wedge pressure (PAWP) ≤15 mmHg (in the absence of pulmonary vein obstruction and/or significant lung disease, PAWP can be replaced by left atrial pressure or, in absence of mitral stenosis, by left ventricular end diastolic pressure)

   AND

   - Indexed PVR index (PVRi) >3 Wood units × m^2.

4. PAH (WHO Group 1), including participants with Down syndrome, of the following etiologies:

   - Idiopathic PAH (IPAH).
   - Heritable PAH (HPAH).
   - PAH associated with congenital heart disease (PAH-aCHD):
     - PAH with coincidental CHD (ie, a small atrial septal defect, ventricular septal defect, or patent ductus arteriosus that does not itself account for the development of elevated PVR) and if approved by the BCAC, refer to Section 10.4).
     - Post-operative PAH (persisting/recurring/developing ≥6 months after repair of CHD).
   - Drug or toxin-induced.
   - PAH associated with HIV.

5. WHO FC II and III.

6. Criterion modified per Amendment 4

   6.1 Participants treated with at least 1 PAH-specific treatment, eg, an ERA and/or a PDE-5 inhibitor/soluble guanylate cyclase stimulator, provided that the treatment dose(s) has been stable for at least 3 months prior to first dose of study intervention.

7. Criterion modified per Amendment 4

   7.1 A female participant of childbearing potential (for a definition refer to Section 10.6) is eligible only if the following apply:

   Has a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test at randomization.

   Agrees to undertake urine pregnancy tests every 4 weeks (± 3 days) during the study and up to at least 30 days after study treatment discontinuation.

   If sexually active, practicing an effective method of birth control consistent with local regulations regarding the use of birth control methods for participants participating in clinical studies until 30 days after last dose of study intervention. Examples of acceptable methods of contraception are located in Section 10.6. It is the responsibility of the investigator to ensure appropriate counselling, including consultation with a specialist (if needed), to the participant and/or parent(s)/LAR(s) on the acceptable method of contraception. To ensure compliance, the study personnel must remind female participants of childbearing potential who are sexually active and their parent(s)/LAR(s) at each visit to use the methods of contraception defined for this study. These reminders must be documented in the source documents.

5.2. Exclusion Criteria

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

Etiology

1. PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease, and/or pulmonary capillary hemangiomatosis.

2. PAH associated with Eisenmenger syndrome.

3. Moderate to large left-to-right shunts[a].

4. Cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, univentricular heart, or pulmonary atresia with ventricular septal defect, as well as participants with Fontan-palliation.

a Left-to-right shunts with a pulmonary-to-systemic flow ratio >1.5 are considered moderate to large (Driscoll 1999). The size and magnitude of left-to-right shunts, if applicable, is assessed by the investigator based on local clinical practice.

5. Criterion modified per Amendment 4

   5.1 Participants with PH due to lung disease and/or hypoxia or history of bronchopulmonary dysplasia. For participants with Down syndrome, exclusion of lung disease and hypoxia causing PH must be documented (eg, normal oxygen saturation in absence of history of lung disease, computed tomography scan, polysomnography, lung function tests).

Treatment and intervention

6. Previous exposure to Uptravi® (selexipag).

7. Treatment with prostacyclin (epoprostenol) or prostacyclin analogs[a] (ie, treprostinil, iloprost, beraprost) within 2 months prior to randomization or scheduled to receive any of these treatments during the study.

8. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before the planned first dose of study intervention or is currently enrolled in an investigational study

9. Treatment with strong and moderate inhibitors of CYP2C8 (eg, gemfibrozil, clopidogrel, deferasirox, teriflunomide) from 2 weeks prior to randomization until the last dose of study intervention +3 days

10. Treatment with inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole) from 2 weeks prior to randomization until the last dose of study intervention + 3 days

11. Any PAH-related surgical intervention planned, or participants listed for organ transplantation related to PAH.

Medical history and co-morbidities

12. Known concomitant life-threatening disease with a life expectancy <12 months

13. History or current suspicion of intussusception or ileus or gastrointestinal obstruction, per the investigator's judgment

14. Uncontrolled thyroid disease, per the investigator's judgment

a Single administration of drugs used for acute vasodilator testing during RHC procedure is allowed (eg, iv/inhaled prostacyclin, inhaled nitric oxide, or oral sildenafil).

15. Hemoglobin or hematocrit <75% of the lower limit of normal range

16. Severe or moderate hepatic impairment, eg, Child-Pugh Class B or C[a].

17. Clinical signs of hypotension that, in the investigator's judgment, would preclude initiation of a PAH-specific therapy

18. Severe renal insufficiency (estimated creatinine clearance <30 mL/min or serum creatinine >221 µmol/L)

19 Severe coronary heart disease or unstable angina as assessed by the investigator

20. Myocardial infarction within the last 6 months prior to enrollment

21. Decompensated cardiac failure if not under close supervision

22. Severe arrhythmias as assessed by the investigator

23. Criterion modified per Amendment 4

    23.1 Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months prior to first dose of study intervention

24. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH

Pregnancy and breastfeeding

25. Pregnant, planning to become pregnant, or lactating

Other categories

26. Known allergies, hypersensitivity, or intolerance to selexipag or its excipients (Selexipag IB)

27. 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

28. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the child (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

29. "Criterion deleted per Amendment 3."

[a] The assessment for hepatic impairment at Screening (Child Pugh Score, refer to Section 10.11) must be fully documented for participants with hepatic impairment as part of medical history and/or clinical signs and evidence (from central and/or local lab) of hepatic impairment.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study (Section 5.4, Screen Failures, describes options for retesting). The required source documentation to support meeting the enrollment criteria are noted in Section 10.4, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

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

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

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once in case the reason for screen-failure is transient. Participants who are re-screened will be assigned a new participant number.

If a participant is re-screened within 42 days of initial screening, only the clinical laboratory assessments must be repeated. In case re-screening occurs >42 days after the initial screening, re-consent is needed and all screening assessments must be performed.

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification number (screening number) and age at screening in years and months.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Designation	Product
Investigational Medicinal Product	Selexipag/matching placebo 200 µg tablets 150 µg/100 µg/50 µg mini-tablets

Designation	Product
	Authorization status in the EU : Authorized for adults: Selexipag

Selexipag and matching placebo is supplied by the sponsor in child-proof bottles containing tablets with the following dosage strengths:

- Bottles of 120 film-coated tablets containing 200 µg of selexipag or matching placebo.
- Bottles of 280 film-coated mini-tablets containing 50 µg of selexipag or matching placebo.

Two additional mini-tablet dosage strengths will be rolled out during the study: 100 µg and 150 µg mini-tablets will replace the concept of combining 50 µg mini-tablets and 200 µg tablets for the body-weight categories ≥9 to <25 kg and ≥25 to <50 kg, respectively:

- Bottles of 280 film-coated mini-tablets containing 100 µg of selexipag or matching placebo.
- Bottles of 280 film-coated mini-tablets containing 150 µg of selexipag or matching placebo.

These additional mini-tablet strengths will become available in participating countries/territories in a staggered approach depending on availability of region-specific stability data. The required number of 100 µg and 150 µg mini-tablets to achieve all dosing levels for participants in the body-weight groups ≥9 to <25 kg and ≥25 to <50 kg are listed in Table 2 and Table 3, respectively.

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

After having verified that the participant meets all inclusion criteria and none of the exclusion criteria (and confirmation of eligibility by the BCAC in participants with aPAH-CHD), the investigator/delegate contacts the Interactive Web Response System (IWRS) at Visit 2 to randomize the participant. The IWRS assigns a randomization number to the participant and assigns the treatment bottle numbers, based on the participant's body-weight category.

The maximum dose allowed to be administered will be 8-fold the corresponding starting dose:

- Body-weight category ≥50 kg: starting dose of 200 µg titrated up to the iMTD or up to a maximum allowed dose of 1,600 µg bid. Participants in this category will receive 200 µg tablets only, or matching placebo (Table 1).
- Body-weight category ≥25 to <50 kg: starting dose of 150 µg titrated up to the iMTD or up to a maximum allowed dose of 1,200 µg bid. Participants in this category will receive a combination of 50 µg mini-tablets and 200 µg tablets or matching placebo (Table 2) OR, once available, 150 µg mini-tablets.
- Body-weight category ≥9 to <25 kg: starting dose of 100 µg titrated up to the iMTD up to a maximum allowed dose of 800 µg bid. Participants in this category will receive either a combination of 50 µg mini-tablets and 200 µg tablets, or 50 µg mini-tablets only, if requested by the investigator, or matching placebo (Table 3) OR, once available, 100 µg mini-tablets. Two study treatment supply options are available:

- **Option 1** will supply the participants with a combination of 200 μg tablets and 50 μg mini-tablets for the lowest overall number of tablets per intake and will be provided via IWRS by default, and
- **Option 2** will supply the participants with 50 μg mini-tablets only upon request by the investigator, in case study treatment intake is possible only with soft food or dispersed in apple/orange juice.

Once 100 μg mini-tablets are available in a respective study region, Option 1 and Option 2 will be replaced by supplying participants with 100 μg mini-tablets.

Study intervention administration will start in the evening of Day 1 and continue thereafter with bid dosing, ie, in the morning and in the evening. During the uptitration period of 12 weeks, it is recommended that the doses are increased weekly in increments equal to the starting dose until the participants reach their iMTD or until a maximum dose corresponding to their baseline body-weight category is achieved. The uptitration steps will be agreed upon during scheduled telephone calls or visits by the investigator or delegate with the participants and/or legally acceptable representatives.

At Week 12 the iMTD for each participant will be determined. This dose should be kept unchanged until Week 16 but can be adjusted for safety or tolerability reasons.

The body-weight category, starting dose, and uptitration scheme determined at Baseline/Enrollment will be kept unchanged until Week 16. After Week 16, if the body-weight category of the participant changes, study intervention can be uptitrated further or downtitrated to the corresponding dose level of the next body-weight category, as deemed appropriate by the investigator (if dose levels overlap between body-weight categories, the dose level may also remain stable).

In addition, irrespective of whether the body-weight category changes or not, after Week 16 the investigators will be allowed to change the participant's study intervention dose further if needed (up to the maximum allowed dose based on body-weight category).

Table 1: Uptitration scheme for participants in body-weight category ≥50 kg

Period	Duration	Dose regimen	Number of 200 µg tablets (bid)
First dose	Day 1 (pm)	200 µg	1
Uptitration	Day 2 (am) to Day 8 (am)	200 µg bid	1
	Day 8 (pm) to Day 15 (am)	400 µg bid*	2
	Day 15 (pm) to Day 22 (am)	600 µg bid*	3
	Day 22 (pm) to Week 4 (am)	800 µg bid*	4
	Week 4 (pm) to Week 5 (am)	1,000 µg bid*	5
	Week 5 (pm) to Week 6 (am)	1,200 µg bid*	6
	Week 6 (pm) to Week 7 (am)	1,400 µg bid*	7
	Week 7 (pm) to Week 8 (am)	1,600 µg bid*	8
Maintenance	From Week 12 throughout the study	iMTD: 200-1,600 µg bid	1–8

bid = twice daily; iMTD = individual maximum tolerated dose.
* Or the highest tolerated dose until Week 12.

Table 2: Uptitration scheme for participants in body-weight category ≥25 to <50 kg

			Combination of 200 µg tablets and 50 µg mini-tablets		150 µg mini-tablets
Period	**Duration**	**Dose regimen**	**Number of 200 µg tablets (bid)**	**Number of 50 µg mini-tablets (bid)**	**Number of 150 µg mini-tablets (bid)**
First dose	Day 1 (pm)	150 µg	-	3	1
Uptitration	Day 2 (am) to Day 8 (am)	150 µg bid	-	3	1
	Day 8 (pm) to Day 15 (am)	300 µg bid*	1	2	2
	Day 15 (pm) to Day 22 (am)	450 µg bid*	2	1	3
	Day 22 (pm) to Week 4 (am)	600 µg bid*	3	-	4
	Week 4 (pm) to Week 5 (am)	750 µg bid*	3	3	5
	Week 5 (pm) to Week 6 (am)	900 µg bid*	4	2	6
	Week 6 (pm) to Week 7 (am)	1,050 µg bid*	5	1	7
	Week 7 (pm) to Week 8 (am)	1,200 µg bid*	6	-	8
Maintenance	From Week 12 throughout the study	iMTD: 150-1,200 µg bid	0–6	0–3	1–8

bid = twice daily; iMTD = individual maximum tolerated dose.

* Or the highest tolerated dose until Week 12.

Once 150 µg mini-tablets are available, combination of 200 µg tablets and 50 µg mini-tablets will be replaced by supplying participants with 150 µg mini-tablets.

Table 3: Uptitration scheme for participants in body-weight category ≥9 to <25 kg

			Option 1		Option 2	100 µg mini-tablets
Period	**Duration**	**Dose regimen**	**Number of 200 µg tablets (bid)**	**Number of 50 µg mini-tablets (bid)**	**Number of 50 µg mini-tablets (bid)**	**Number of 100 µg mini-tablets**
First dose	Day 1 in the evening (pm)	100 µg	-	2	2	1
Uptitration	Day 2 am to Day 8 am	100 µg bid	-	2	2	1
	Day 8 pm to Day 15 am	200 µg bid*	1	-	4	2
	Day 15 pm to Day 22 am	300 µg bid*	1	2	6	3
	Day 22 pm to Week 4 am	400 µg bid*	2	-	8	4
	Week 4 pm to Week 5 am	500 µg bid*	2	2	10	5
	Week 5 pm to Week 6 am	600 µg bid*	3	-	12	6
	Week 6 pm to Week 7 am	700 µg bid*	3	2	14	7
	Week 7 pm to Week 8 am	800 µg bid*	4	-	16	8
Maintenance	From Week 12 throughout the study	iMTD: 100–800 µg bid	1–4	0 or 2	2–16	1–8

bid = twice daily; iMTD = individual maximum tolerated dose.
* Or the highest tolerated dose until Week 12.
Once 100 µg mini-tablets are available, Option 1 and Option 2 will be replaced by supplying participants with 100 µg mini-tablets.

Study intervention is administered orally bid with an interval of approximately 12 hours.

Tablets can be administered via 1 of 3 options:

- Swallowing the tablets/mini-tablets whole with water.
- Swallowing tablets/mini-tablets with soft food.
- Dispersing mini-tablets in apple or orange juice.

Tablets or mini-tablets should not be crushed, split, or chewed.

Administration of tablets with soft-food

Participants can take 200 µg tablets and 50 µg, 100 µg, and 150 µg mini-tablets (refer to Table 3) with soft food (ie, yoghurt, apple sauce/puree/mousse, or mashed banana) according to the following instructions:

a) Take the instructed number of tablets as shown in the respective protocol uptitration scheme.

   i. For 50 µg and 100 µg mini-tablets: place the instructed number of mini-tablets as shown in uptitration scheme on a spoon.

   ii. For 150 µg mini-tablets: place up to 5 mini-tablets at a time on a spoon.

   iii. For 200 µg tablets: place up to 4 tablets at a time on a spoon.

b) Place enough soft food onto the spoon to completely cover the tablet(s). Multiple spoons of tablets and soft food may be used, if required.

c) All the soft food with the tablets should be consumed by the participant to ensure administration of the complete dose.

d) After the soft food is consumed, check the spoon to ensure all tablets have been taken (add more soft food, if necessary).

Administration of mini-tablets with juices

The 50 µg, 100 µg, and 150 µg mini-tablets can also be administered by dispersing in apple- or orange-juice according to the following instructions:

a) Place the instructed number of mini-tablets as shown in uptitration scheme in a beverage recipient made of glass or porcelain.

   i. The minimal volume of beverage to disperse the 50 µg mini-tablet, must be 1 mL per mini-tablet.

   ii. The minimal volume of beverage to disperse 100 µg and 150 µg mini-tablets, must be 2 mL and 3 mL per mini-tablet, respectively.

b) Disperse the mini-tablets by adding apple- or orange-juice to the mini-tablets and subsequently gently swirling the drinking recipient manually.

c) After the liquid is consumed, check the recipient to ensure all mini-tablets have been taken (add more beverage, if necessary).

At the beginning of each uptitration phase, participants will be advised to take the first dose in the evening to reduce the burden of potentially occurring events such as headache, jaw pain, flushing, and nausea. The study intervention can be taken with or without food (ie, a meal), although tolerability may improve when selexipag is taken with food.

If a participant has tolerability issues and experiences adverse reactions reflecting the mode of action for selexipag (refer to Section 7.1), that cannot be managed with symptomatic treatment, the dose can remain the same without further uptitration (pause in uptitration). Uptitration can be resumed after the pause, or the dose can be reduced to the previous dose level. The decision to pause uptitration, uptitrate or downtitrate study intervention, or to permanently discontinue study intervention will be based on the investigator's medical judgment (refer to Section 7.1).

If a dose of selexipag is missed, the participant should take a dose as soon as possible unless the next scheduled dose is within the next 6 hours.

At any time during the double-blind treatment period, study intervention interruptions (eg, missed doses for any reason) of 3 days (ie, at least 6 consecutive scheduled study treatment administrations) or more (but less than 14 consecutive days; refer to Section 7.1) will require a new uptitration according to the scheme from Day 1 (as specified in Table 1, Table 2, and Table 3).

On visits when PK samples are scheduled (twice during the maintenance period), study intervention morning dose must be taken at the site after the trough PK sampling under investigator site staff supervision.

Study site personnel will instruct participants and/or their parent(s)/LAR(s) about how to capture the study intervention administration in an eDiary and how to store the study intervention for at-home use.

Study intervention will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

For details on optional treatment with the Auxiliary Medicinal Product (AxMP) bosentan following disease progression, refer to Section 10.16. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label. Refer to the site Investigational Product binder/study site

investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Accountability

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

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. Information about handling and destruction of study intervention is provided in the study site Investigational Product binder.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups (placebo or selexipag) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by WHO FC (II vs III) at randomization, and by PAH-specific treatment (monotherapy vs combination therapy). The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

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

Participants who have had their study intervention assignment unblinded should discontinue study intervention and continue to return for scheduled evaluations.

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

In rare circumstances when a potential safety issue that may impact the overall benefit-risk assessment of the investigational product has been identified in this study, selected sponsor personnel may be unblinded to safety-related data in order to investigate the safety issue and determine if additional actions are required. The safety data should be kept blinded to any personnel not essential to the safety review.

If other rare, unforeseen circumstances arise that may necessitate unblinding of selected sponsor personnel, these will be assessed and documented on a case-by-case basis. The data should be kept blinded to any personnel not essential to the review or investigation of the safety event.

The study team will be blinded until database lock for Analysis 2. An independent submission team will be unblinded to the data and perform Analysis 1 CCI [redacted] Details will be documented in a separate charter, which will be finalized prior to Analysis 1.

6.4. Study Intervention Compliance

Study intervention compliance is based on study intervention accountability (refer to Section 6.2). Site personnel will enter the number of tablets returned in IWRS. Study intervention compliance will be calculated by the sponsor using the below formula:

$$\text{Compliance} = \frac{\text{Number of tablets dispensed} - \text{Number of tablets returned}}{\text{Total number of tablets that should have been taken during the period}^{*}} \times 100$$

* The period is defined as the number of days of treatment from the date of dispensation of study intervention until the next accountability visit. The number of tablets that should have been taken should be calculated on a participant basis, based on the investigator's prescription.

A mobile hand-held electronic device will be provided to the participant/LAR(s) to document daily study intervention intake (eDiary). Between visits and overall study compliance is expected to be between 80% and 120%. During the course of the study, the investigator or designated study site-personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the study intervention.

6.5. Concomitant Therapy

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the CRF. Previous therapy must be recorded in the CRF if discontinued less than 42 days prior to the signing of the ICF. Recorded information will include a description of the type of therapy, duration of use (treatment start and end date), dosing regimen, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

Allowed PAH-related Concomitant Therapy

PAH-specific concomitant therapies such as ERAs, PDE-5 inhibitors, and soluble guanylate cyclase stimulator in mono- or combination therapy as per local standard-of-care are permitted. The dose must have been stable for at least 3 months prior to the first dose of study intervention. Dose adjustments for body weight changes are allowed.

Treatment with diuretics is permitted. The dose must have been stable for at least 1 month prior to the first dose of study intervention.

Single administration of medications used for acute vasodilator testing during RHC procedure is allowed (eg, iv/inhaled prostacyclin or inhaled nitric oxide or oral sildenafil).

Prohibited Concomitant Therapy

Strong and moderate inhibitors of CYP2C8 (eg, gemfibrozil, clopidogrel, deferasirox, teriflunomide) and inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole) are prohibited from 2 weeks prior to enrollment until the last dose of study intervention +3 days.

As selexipag and its active metabolite ACT-333679 are IP receptor agonists, prostacyclin (epoprostenol) and prostacyclin analogs (ie, treprostinil, iloprost, beraprost – except for acute vasodilator testing during RHC procedure) are prohibited from 2 months prior to randomization until the last dose of study intervention +3 days or PAH worsening during the double-blind treatment period.

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

6.6. Dose Modification

Any study intervention dose/dosage adjustment should be overseen by medically-qualified study site personnel (principal or sub-investigator unless an immediate safety risk appears to be present).

Dose adjustments must follow the titration instructions (refer to Section 6.1).

6.7. Treatment of Overdose

For this study, an overdose is defined by the intake of:

- any single study intervention dose greater than 1,600 µg or a total daily dose greater than 3,200 µg (a child with body-weight category ≥50 kg);
- any single study intervention dose greater than 1,200 µg or a total daily dose greater than 2,400 µg (a child with body-weight category ≥25 to <50 kg);
- any single study intervention selexipag dose greater than 800 µg or a total daily dose greater than 1,600 µg (a child with body-weight category ≥9 to <25 kg).

Isolated cases of overdose up to 3,200 µg have been previously reported in adults. Mild, transient nausea was the only reported consequence.

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

- Contact the sponsor immediately.
- Evaluate the participant to determine, in consultation with the sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until selexipag can no longer be detected systemically (at least 3 days).
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the sponsor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
- Institute supportive measures as clinically required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein bound.

6.8. Intervention After the End of the Study

After the participant's study completion, the investigator/delegate will inform the sponsor, and explain what treatment(s)/medical care is necessary and available according to local regulations.

If considered by the investigator to be in the best interests of the participant, the investigator can ask the sponsor to provide participants who completed the study and did not prematurely discontinue study treatment with selexipag. In this case, selexipag can be provided until access to commercial selexipag is possible in this indication in the participant's country/territory of residence (according to local regulatory requirements), until selexipag can be accessed through another source in the country/territory where he/she is living, or until the sponsor terminates clinical development of selexipag in this indication.

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

At the end of their participation in the OLEP, participants who benefit from the study treatment (selexipag) will receive continued access to selexipag via the following options:

- Switch to commercial Uptravi (applicable to participants who live in a country/territory where selexipag is commercially available and approved for the treatment of pediatric participants with PAH),
- Switch to a PTA program which will be set up for participants who reside in countries where selexipag is not yet commercially available, if allowed as per local regulations,
- Switch to an open-label study for long-term follow-up (applicable for participants who live in a country/territory where the conduct of such a study is approved by the local health authorities and where the 2 options above are not applicable).

For participants rolling over to post-trial access (PTA) or the subsequent open-label study, the enrollment must occur on the day of the LSV of SALTO, ie, EOS call which corresponds to LSV, to avoid selexipag treatment interruption. For participants who complete the study treatment and who are eligible for a PTA or the subsequent open-label study, the posttreatment safety follow-up period will be waived.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention. The following selexipag-specific criteria should be considered by the investigator:

- 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 include: headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing. In adult patients 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).

However, if a participant reaches a dose that cannot be tolerated, the investigator should follow the instructions given in Section 6.1.

- Gastrointestinal ileus or obstruction

  In selexipag preclinical studies in juvenile dogs, intestinal intussusception due to prostacyclin related effects on intestinal motility was observed sporadically. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific propensity of dogs to develop intussusception, this finding is not considered relevant for adult humans. The clinical relevance of these findings for the pediatric population <18 years is unknown.

  The investigator is asked to inform the parents and participants and provide guidance that they should seek immediate medical evaluation if, at any time during study treatment, the participant experiences clinical signs compatible with gastrointestinal ileus or obstruction (eg, sudden severe persisting abdominal pain with episodes re-appearing in shorter intervals, stool mixed with blood and mucus [also referred as red currant jelly stool], extensive diarrhea and/or vomiting, lump in abdomen, fever, anorexia, and lethargy).

  If the diagnosis of intussusception is confirmed, the study intervention must be permanently discontinued.

- Hyperthyroidism

  Hyperthyroidism has been observed in 1% of the participants treated with selexipag in the GRIPHON study (Selexipag IB).

  The investigator will be asked to inform the participants and parents and provide guidance that they should be proactive and report if, at any time during study treatment, the participant experiences clinical signs of hyperthyroidism (eg, sudden weight loss even if appetite and the amount and type of food remain the same or even increased), tachycardia, arrhythmia or palpitations, nervousness, anxiety and irritability, tremor, sweating, an enlarged thyroid gland, difficulty sleeping).

  If the participant experiences new or worsening of pre-existing hyperthyroidism during the course of treatment with study intervention that, in the opinion of the investigator, cannot be adequately controlled with anti-thyroid medications, the study intervention must be permanently discontinued and the participant monitored until resolution of this condition.

- Hepatic impairment

  If the investigator becomes aware that a participant has developed moderate or severe hepatic impairment (Child-Pugh B or C) at any time during the study, the study intervention must be permanently discontinued. For patients who develop hepatic impairment at any time during the study, the assessment for hepatic impairment (Child-Pugh Score) must be performed and fully documented.

- Pulmonary edema due to pulmonary veno-occlusive disease (PVOD)

  If a participant develops pulmonary edema due to previously undiagnosed PVOD, the study intervention must be permanently discontinued.

- Treatment with prostacyclin/prostacyclin analogs

  If treatment with prostacyclin (epoprostenol) or prostacyclin analogs (ie, treprostinil, iloprost, beraprost) is initiated at any time during the study (except for acute vasodilator testing during RHC procedure), the study intervention must be permanently discontinued.

- The participant becomes pregnant.

  Refer to Section 10.6, Contraceptive and Barrier Guidance.

Study intervention interruptions exceeding 14 consecutive days must lead to permanent discontinuation of study intervention. In that case, the EOT visit must occur within 10 days of the discontinuation criterion being met.

If a participant discontinues study intervention for any reason before the end of the double-blind treatment period, assessments should be obtained and scheduled assessments should be continued as indicated in the Schedule of Activities.

7.2. Temporary Discontinuation

For participants who are unable to tolerate the protocol-specified dosing scheme, dose adjustments should follow the instructions in the uptitration scheme (refer to Section 6.1). Study intervention may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons.

If, at any time during the double-blind treatment period, the participant experiences an AE (other than those listed in Section 7.1) in response to which their dose is reduced, re-titration to the iMTD (refer to Section 6.1) may be resumed, per the investigator's medical judgment.

Participants and parent(s)/LAR(s) must be instructed to immediately inform the investigator when study intervention is interrupted by the participant/parent/LAR(s) for any reason.

If a dose of study intervention (selexipag/placebo or selexipag open-label) is missed, participants should take a dose as soon as possible unless the next dose is scheduled within the next 6 hours.

Interruptions of 1 day or more must be recorded in the source documents and in the CRF.

At any time during the double-blind and open-label treatment periods, study intervention interruptions (eg, missed doses for any reason) of 3 days (ie, at least 6 consecutive scheduled study treatment administrations) or more (but less than 14 consecutive days, refer to Section 7.1) will require a new uptitration according to the scheme from Day 1.

7.3. Participant Discontinuation/Withdrawal From the Study

A participant will not be automatically withdrawn from the study if they have to discontinue study intervention before the end of the intervention regimen.

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

- Lost to follow-up.
- Withdrawal of consent/assent.
- Death.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. If a participant discontinues study intervention and withdraws from the study before the end of the double-blind intervention phase, end-of-intervention and post-intervention assessments should be obtained. If participants/parent(s)/LAR(s) withdraw from the study but do not withdraw the consent/assent to provide limited information until the study closure, safety follow-up and survival follow-up information is collected in the CRF (refer to Section 8.2.7). If the reason for withdrawal from the study is withdrawal of consent/assent, then no additional assessments are allowed.

7.4. Lost to Follow-up

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

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.

Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Sections 1.3.1, 1.3.2, 1.3.3, and 1.3.4) summarizes the frequency and timing of efficacy, PK, and safety measurements applicable to this study.

All PRO/QoL assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant's perceptions.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: Safety assessments, PK sampling efficacy assessments, other assessments. Actual dates will be recorded in the source documentation and CRF.

Up to Week 16, a total of approximately 24 mL of blood are required for hematology and clinical chemistry testing. After Week 16, approximately 4.8 mL of blood are required per visit. In addition, 1.2 mL of blood are required in 2 instances for PK sampling. Refer to the laboratory manual for the required blood volumes per test.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form.

Refer to the Schedule of Activities (Sections 1.3.1, 1.3.2, 1.3.3, and 1.3.4) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure for selexipag
- Summarized Investigational Medicinal Product Dossier/Summary of Product Characteristics/Investigator's Brochure for bosentan
- Investigational Product binder with study site investigational product and procedures manual
- Site tablets, eDiaries and instructions for use
- Accelerometry guidelines
- Echocardiography manual
- ECG manual
- Instructions on how to access eCRFs
- Wallet cards for study participant/parent
- Independent ethics committee/institutional review board (IEC/IRB)-approved recruitment and retention tools

- IRB-approved informed consent and assent forms
- Laboratory manual, requisition forms and sampling supplies.
- IWRS manual.
- eCRF completion guidelines.
- SAE forms and completion guidelines.
- Pregnancy notification form and follow-up forms.
- Product Quality Complaint form.
- 6MWT starter kit.
- Yellow light lamps (for PK sample processing, refer to Section 8.7).

8.1. Screening and Baseline Assessments

8.1.1. Demographics

Demographic and baseline characteristic data are recorded in the CRF for all participants and include: age, sex, race, ethnicity (where local regulations permit).

8.1.2. Medical History

Relevant medical history/current medical conditions present before signing the ICF will be recorded in the CRF and include

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

Where possible, diagnoses and not symptoms will be recorded.

The condition being studied, ie, PAH, and related signs and symptoms, will not be recorded as medical history but will be recorded on dedicated CRF pages (refer to Section 8.1.3).

8.1.3. Baseline Disease Characteristics and Baseline Narrative

PAH etiology, PAH diagnosis (mPAP, PAWP [or left atrial pressure or left ventricular end-diastolic pressure], PVRi values assessed by RHC and date of diagnosis), and date of first observed/assumed PAH symptoms will be recorded in the CRF.

For participants with PAH with coincidental CHD, ie, atrial septal defect, ventricular septal defect or patent ductus arteriosus which themselves are not considered to account for the development of elevated PVR, the investigator submits relevant clinical, RHC and echocardiography data to the BCAC for review and approval (refer to Section 10.4). Participants will only be randomized after

the BCAC confirms the diagnosis of PAH associated with coincidental CHD, provided all other entry criteria are confirmed.

Investigators will be requested to describe the condition of the participant at baseline. This baseline narrative will be provided to the Sponsor for overview of document completeness and to CEC for assessing a potential primary endpoint event in case of disease progression.

8.1.4. PAH related Treatments and Interventions

Previous treatments and interventions related to PAH (ie, PAH-specific medications such as ERAs, PAH non-specific treatment such as inotropes, diuretics, anticoagulants, oxygen, etc) will be recorded in the CRF if stopped less than 48 weeks prior to signing informed consent.

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

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

Survival Follow-up Period: For participants who prematurely discontinue study intervention, PAH-specific treatments administered up to EOS (ie, last survival follow-up contact) will be recorded in the CRF.

8.2. Efficacy Assessments

8.2.1. Monitoring of Disease Progression

Worsening of the clinical condition of a participant can occur at any time during the study. In all participants, assessment and reporting of any further disease progression will continue until the EOS. Parent(s)/caregiver(s) are instructed to contact the investigator immediately if the participant deteriorates to arrange for a visit (scheduled or un-scheduled, refer to the Schedule of Activities) if needed.

In case of suspected disease progression (eg, signs/symptoms denoting PAH worsening or deterioration of WHO FC) the investigator determines the main and contributing causes for worsening as per local practice. If applicable, the investigator reports which components of the primary efficacy endpoint are met.

In case the participant is hospitalized at a center other than the investigational site, the investigator will collect the above data as available by contacting the treating center, will request the hospital discharge summary and the autopsy report (if applicable), and will record disease progression in the CRF.

The following data related to the primary and secondary efficacy endpoints of PAH disease progression (refer to Section 3) will be recorded in the CRF:

- Death, primary cause, and date of death.

- PAH-related non-pharmacological interventions (such as atrial septostomy, etc) and the date and reason for the intervention (refer to Section 8.1.4).
- Medications related to PAH (such as PAH-specific medications, diuretics, and oxygen) (refer to Sections 6.5 and 8.1.4).
- For hospitalizations, the admission/discharge date together with the reason for hospitalization is recorded on the AE CRF page and on the dedicated Clinical Worsening CRF page (if cause is related to PAH).
- Signs/symptoms denoting PAH-worsening together with their onset/resolution date as well as WHO FC.

8.2.1.1. Participant narrative

In case of suspected disease progression, the investigator or delegate creates a participant narrative describing the suspected disease progression event based on the assessments made and any additional relevant information in the medical chart to help the CEC to assess the event as a Primary Endpoint Event (refer to Section 8.2.1.3). The investigator will use the participant narrative written at Visit 2 (refer to Section 8.1.3) as baseline reference.

8.2.1.2. Signs and symptoms of PAH

Investigators will verify the presence/absence of predefined signs and symptoms (refer to Section 3) denoting clinical worsening of PAH.

The presence and absence of signs/symptoms will be recorded in the CRF. The date of new onset or worsening will also be recorded in the CRF.

The occurrence of a new or worsening sign/symptom will be recorded as an AE in the CRF.

If there is syncope or at least 2 new or worsening signs/symptoms the disease progression will be recorded in the CRF and the investigator will perform further exams to determine the cause.

8.2.1.3. Independent CEC Review of Suspected Disease Progression Events

The investigator or delegate will provide the narratives (participant condition at baseline (refer to Section 8.1.3) and at disease progression (refer to Section 8.2.1.1) and a copy of the baseline and follow-up echocardiography report as well as other relevant reports (such as hospital discharge letter, RHC report, etc) that support the assessment of disease progression to the CEC.

If needed, the CEC-coordinator will ensure that these reports are translated into English. The CEC-coordinator must ensure that narratives and copies of source data are blinded for participant identifiers (such as initials, birth dates, address, telephone numbers, etc), and do not reveal the study treatment, such as prostacyclin-related AEs (refer to Section 7.1), the investigational site or country/territory. The CEC-coordinator will provide the reports and narratives to the CEC.

If the CEC requests further data or clarification (eg, follow-up narrative), the CEC-coordinator will contact the respective investigator and forward the additional information to the CEC, if available.

The study team may consult the CEC for events that were not reported as suspected disease progression by the investigator. For further details regarding the role of the CEC refer to Section 10.4, Section 3, and to the CEC-Charter.

For all participants, assessment and reporting of any further disease progression will continue until the EOS. All disease progression events reported during the double-blind treatment period will be adjudicated by the CEC.

8.2.2. Functional Class

WHO FC (refer to Section 10.8) and Panama FC (refer to Section 10.9) will be recorded in the CRF. The Panama FC is tailored for children up to 16 years of age (Lammers 2011) and thus its assessment will discontinue once children reach >16 years of age.

If there is worsening in the WHO FC, refer to Section 8.2.1 for reporting of disease progression. Worsening in Panama FC does not qualify for reporting disease progression; however, the data will be provided to the CEC as supportive data.

8.2.3. NT-proBNP

The quantification of NT-proBNP serum concentrations will be performed by the central laboratory. Central laboratory data will be transferred from the central laboratory to the clinical database.

Due to circadian fluctuations of NT-proBNP levels, the blood sample for NT-proBNP should preferably be taken at the same time in the day at each scheduled visit.

The procedure for collection and analysis of NT-proBNP is described in the Laboratory Manual.

8.2.4. Echocardiography

Local Reading: An echocardiography (and/or Doppler) to document the severity of PAH (assessing, eg, pericardial effusion, right ventricular pressure, inferior vena cava size) will be performed as per local practice during screening. The data will be analyzed locally. In the presence of suspected disease progression, the same parameters will be assessed as a follow-up echocardiography (and/or Doppler) to document whether there are any changes since baseline. In this case, the reports of the baseline and of the follow-up echocardiography will be sent to the CEC-coordinator who will provide this as supportive data to the CEC (refer to Section 8.2.1).

In addition, for participants with PAH with coincidental shunts, local echocardiography will be used to confirm eligibility and must be submitted digitally to the BCAC (refer to Sections 8.1.3 and 10.4).

Central Reading: The following parameters will be assessed as described in the AC-065A310 image acquisition guidelines:

- Right ventricular systolic pressure.
- Tricuspid annular plane systolic excursion.

- Pulmonary artery acceleration time.
- Left ventricular eccentricity index.
- Right atrial area index (from apical 4-chamber view).
- Tricuspid annular diameter (from apical 4-chamber view).

The investigator (or delegate) will submit echocardiography data digitally, together with a Data Transmittal Form to the Central Echocardiography Contract Research Organization (CRO) as instructed in the Echocardiography Manual. The data will be analyzed centrally by the CRO and transferred electronically to the clinical database. The CRO conducting the central reading will also receive the clinical data necessary for the interpretation of the images such as body weight/height and heart rate.

8.2.5. Physical Activity/Accelerometry

Physical activity (counts/minutes) of participants will be assessed with an accelerometer. Accelerometer devices will be provided to the investigational site before the start of the study.

The participant will collect data wearing the accelerometer during the 10 to 14 consecutive days before respective visits. The baseline assessment is performed at any time between Visit 1 and Visit 2. If, for any reason, data are not collected before respective study visits, the participant will collect the data during the 10 to 14 days following the visit. This will allow collecting data during weekdays and weekend days and will provide a reliable estimate of the usual physical activity of the participant.

At Visit 1 the investigator (or delegate) will instruct parent(s)/LAR(s) and developmentally capable participants on how and when to wear the accelerometer (refer to Accelerometry Guidelines). The accelerometer will be worn during the participant's waking hours. The device may be removed during the night rest and during activities when the device could get wet (eg, showering, bathing, swimming).

The parent(s)/LAR(s) or participants will bring the device to the study site at site visits and the investigator (or delegate) will transfer the data to the accelerometry service provider as instructed in the Accelerometry Guidelines. For participants who are not eligible to participate in the study, data (if collected during screening) will be transferred to the service provider. At Week 48, the accelerometer will not be returned to the participant. After successful data transfer, the device will be re-set and can be re-used by another study participant.

The accelerometry service provider will read daily counts/minutes and analyze duration of daytime activity and time (minutes) spent in moderate-to-vigorous physical activity as compared to time spent in sedentary, light, moderate, vigorous physical activity. These data will be transferred to the clinical database.

The data received will be monitored for compliance. Should corrective actions be necessary, participants may be contacted by the site staff.

8.2.6. 6-Minute Walk Distance

The 6MWT is a non-encouraged test that measures the distance covered by the participant during a 6-minute walk. Guidelines are provided in the AC-065A310/SALTO 6MWT Guidance.

The 6MWD will be assessed in those participants from ≥6 to <18 years who understand and are able to perform the test correctly (Douwes 2015; Takatsuki 2013). Test results and the time of assessment will be recorded in the CRF.

8.2.7. Survival Follow-up

Participants for whom parent(s)/LAR(s) have withdrawn the consent/assent from study intervention and who do not continue with the planned schedule of assessments (regular study visits) and agree to be contacted for the survival follow-up (refer to Section 7.3) will be contacted at least yearly by the study investigator. Survival follow-up contacts will be performed within 6 weeks after the announcement of each Analysis Time point. The contact made after the last Analysis Time point performed will be considered the EOS.

The survival follow-up contact includes assessment of:

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

The investigator will collect these data through direct contact with parent(s)/LAR(s) or participants as well as indirectly via the treating physician. Data can be collected via telephone call, site visit or through written communication (eg, letter) and will be recorded in the CRF.

8.2.8. Right Heart Catheterization

RHC is not a mandatory study specific assessment, however, if RHCs are performed during the study for any medical reason, as judged by the investigator, results should be recorded in the CRF.

8.3. Safety Assessments

Details regarding the IDMC are provided in Committees Structure in Section 10.4, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.6, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Section 10.5, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached and is to be documented in the source notes.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities:

8.3.1. Physical Examination

At Screening, the physical examination includes:

- General appearance,
- Head, ears, eyes, nose, throat,
- Cardiovascular,
- Respiratory,
- Gastrointestinal,
- Lymphatic,
- Genitourinary,
- Skin,
- Extremities, and
- Nervous system.

At subsequent visits, physical examination includes the examination of

- General appearance,
- Cardiovascular, and
- Respiratory systems only.

Other exams may 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.

Clinically relevant findings that are present prior to the signing of the ICF must be recorded on the Medical History CRF page.

Physical examination findings made after the signing of the ICF that meet the definition of an AE (refer to Section 8.6) must be recorded in the CRF.

Height will be measured without shoes. Body weight will be measured in indoor clothing but without shoes.

8.3.2. Vital Signs

Vital signs include SBP and diastolic BP (DBP) and heart rate. Vital signs are measured non-invasively. It is recommended that vital signs are measured after the participant has rested at least 5 minutes (eg, sitting). If applicable, vital signs are measured before any invasive assessment (such as blood draw).

SBP and DBP will be measured in a supine or sitting position. It is recommended to allow the participant to rest in a quiet setting without distractions (eg, television, cell phones) for at least 5 minutes, and to use the same position (supine or sitting) throughout the study for an individual participant.

It is recommended that the same type of device is used throughout the study for an individual participant. In addition, it is recommended to measure BP on the same arm for an individual participant throughout the study.

Vital signs are recorded in the CRF.

8.3.3. Electrocardiogram (ECG)

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures are recommended to be performed in the following order: ECG(s), vital signs, blood draw.

Clinically relevant ECG findings observed after Screening or that worsened during the study must be reported as AEs as appropriate (refer to Section 8.6).

A central ECG service will be used for ECG evaluation. Details about the collection of ECG data and the reporting of results and abnormalities can be found in the ECG manual provided to the investigator.

8.3.4. Tanner Stage

According to ICH E11, as medicinal products may affect growth and development in children, safety surveillance should encompass evaluation of maturation. Per CHMP Paediatric addendum to the PAH guidelines (EMA/CHMP/213972/2010), the sexual maturation of pediatric participants in long-term studies is of particular importance. Therefore, the Tanner stage (refer to Section 10.12) will be assessed at regular time points during the study.

Tanner stage is assessed in female participants ≥8 years of age and in male participants ≥9 years of age either at study start or at the first scheduled site visit as soon as they reach that age during the study. Tanner stage assessment is no longer required once full sexual maturation is reached (if applicable before EOT). Assessment of pubertal Tanner stage by parents or self-assessment by participants may be allowed by the study investigator. In this case, the investigator will instruct and assists parents/participants on how this should be assessed at each time of the scheduled assessment.

The Tanner stages of puberty in females are based on breast size and shape and pubic hair distribution. The Tanner stages of puberty in males are based on the development of the genitalia and pubic hair distribution (Blondell 1999; Marshall 1969; Marshall 1970). Actual age at milestone attainment may vary among individuals and among different study populations.

Tanner stage is recorded in the CRF.

8.3.5. Childbearing Potential

Guidance on the definition of childbearing potential is provided in in Section 10.6.

For female participants of childbearing potential, the study personnel will verify at each visit whether the participant has or plans to become sexually active. If confirmed, the study personnel will counsel the participant on the appropriate methods of contraception (refer to Section 10.6).

Whether or not a female participant is of childbearing potential and the reason for not being of childbearing potential will be recorded in the CRF. As soon as a participant becomes of childbearing potential, site staff will also record this in the electronic clinical outcome assessment (eCOA) system to trigger every 4 weeks (± 3 days) urine pregnancy test result recording in the eDiary.

8.3.6. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry (including pregnancy testing and thyroid markers) and hematology will be collected as noted in Section 10.3, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the medical history (if during Screening) or AE section of the CRF. The laboratory reports must be signed and dated and filed with the source documents.

8.4. Quality of Life Assessments

In a subset of countries/territories, QoL will be assessed and completed on a mobile electronic device (site tablet). The data from the mobile device will be collected by the vendor and shared with the sponsor and site staff.

The PedsQL™ Pediatric Quality of Life Inventory version 4.0 short form (SF 15) will assess the general physical, emotional, social, and school functioning (15 questions) (refer to Section 10.13).

The “heart problems and treatment” component of the PedsQL™ Cardiac Module version 3.0 and the “general fatigue” component of the PedsQL™ Multidimensional Fatigue Scale standard version questionnaires assess:

- Heart problems and problems with treatment (7 questions) (refer to Section 10.14), and
- Problems with general fatigue (6 questions) (refer to Section 10.15).

The questionnaires are adapted for different age groups: toddlers (2 to 4 years of age), young children (5 to 7 years of age), children (8 to12 years of age) and adolescents (13 to 18 years of age).

For toddlers, a parent or LAR will complete the QoL questionnaire and rate each item using a 5-point Likert scale per item. For young children, a site study person will read the questions to them and ask them to point to a 3-scale smiley score (Young Child Report). This score will then be marked by the site study person. In the two oldest age categories, participants will complete

their QoL questionnaire using a 5-point Likert scale for each item. A parent/LAR additionally will complete the QoL questionnaire (Parent Report) adapted to rate their young child, child or adolescent, also using a 5-point Likert scale per item. For participants over 8 years of age who are unable to complete questionnaires per the judgment of investigator or designee, only Parent Reports will be collected. Participants and parent(s)/LAR(s) will be asked to rate the QoL considering the 1-month period preceding the completion of the questionnaire.

The QoL questionnaires will be completed in a subset of participating countries/territories for which a validated questionnaire is available and IRB/EC approved.

- The Parent Report (QoL questionnaire) will preferably be completed by the same parent/LAR at all time points for an individual participant
- If the participant changes age category during the conduct of the study, the same questionnaire as at Visit 2 will continue to be completed.

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

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

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

8.5. Palatability and Acceptability

The palatability of the study intervention formulation will be assessed at the visits indicated in the Schedule of Activities using a 5-point facial hedonic scale. The palatability scale will be completed on a mobile electronic device (site tablet).

For children who are not able to comply with the instructions of the test, palatability will be indirectly assessed by the participants' parent(s) or LAR(s) or study site personnel (refer to Section 10.10).

The acceptability of the study intervention formulation will be assessed using a 3-point categorical scale to determine whether the child swallowed the medication at the visits indicated in the assessment schedule. The acceptability scale will be completed on a mobile electronic device (site tablet).

For all participants, parent(s) or LAR(s) or study site personnel will be asked, following the study drug intake, whether the child swallowed the medication (a) fully, (b) partially or (c) not at all.

8.6. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information.

Adverse events will be reported by the participant/parent/LAR for the duration of the study. No anticipated events have been defined.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.5, Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.6.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations (refer to Section 10.5), whether serious or non-serious, will be reported on specific AE pages of the CRF throughout the study from signing of the ICF onwards until the EOS visit (refer to Section 4.4) or date of last contact (refer to Section 7.4).

Serious Adverse Events

All SAEs, as well as product quality complaints (PQC), occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the event.

SAEs, including those spontaneously reported to the investigator throughout the study from signing of the ICF onwards until the EOS visit or date of last contact (refer to Sections 4.4 and 7.4), must be reported on AE pages of the CRF and on the SAE Form, irrespective of the study intervention received by the participant and whether or not this event is considered by the investigator to be related to study intervention.

The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events of aminotransferase ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

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

8.6.2. Follow-up of Adverse Events and Serious 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 PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.6.3. Regulatory Reporting Requirements for Serious Adverse Events

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

8.6.4. Pregnancy

All initial reports of pregnancy in female participants or female partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention (refer to Section 7.1).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the newborn will be required. The duration of this follow-up will depend on the clinical conditions of the newborn and may be extended until discharge from hospital, when applicable.

8.7. Pharmacokinetics

Plasma samples will be used to evaluate the PK of selexipag and its metabolite ACT-333679 (JNJ-68006861) using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method under the supervision of the sponsor. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Trough PK samples will be collected prior to administration of the morning dose of study invention twice during the maintenance period (refer to Section 4.1). Prior to any PK sample collection, the participant should have been for at least 3 days on the same dose in order to reach steady-state.

For the participant's convenience, an overnight stay at the site or a hotel may be required before collection of the PK sample.

In total, 2 PK samples (1.2 mL blood/sample) will be collected per participant throughout the study.

Procedure for sampling

To prevent degradation of selexipag and its metabolites in the plasma samples, exposure of the plasma to light should be minimized, and the whole sample preparation should be conducted under yellow light.

Blood samples of 1.2 mL will be collected by direct venipuncture or via an iv catheter into spray-dried lithium heparin-containing Greiner Vacuettes®. Immediately following collection, the tube will be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution, and immediately cooled on ice. Within 30 minutes of collection, the blood samples will be centrifuged at approximately 1,500×g/3,000 revolutions per minute for 10 minutes at 4°C (39.2°F).

The resulting plasma (approximately 0.5 mL plasma) will be transferred into a single, labeled opaque polypropylene tube. Avoid carryover of erythrocytes.

All samples will be stored in an upright position at ≤-18°C (-0.4°F).

The date and exact actual clock time of collection of each blood sample will be recorded in the CRF as well as the date and exact actual clock for the preceding dose of study intervention.

8.7.1. Pharmacokinetic Parameters and Evaluations

Parameters

Trough plasma concentration at steady-state ($C_{trough,ss}$) is defined as the plasma concentration just prior to the morning dose, with the last study intervention administration one day prior to the PK sampling. Steady-state is considered achieved if the participant has received a stable dose for at least 3 days prior to collection of the plasma sample.

If considered appropriate, plasma concentration of selexipag and its active metabolite ACT-333679 may be analyzed using population PK analysis.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or delegated to a CRO under the responsibility of the sponsor. Unblinded analyses for the IDMC will be performed by an independent, unblinded statistical support group (ISSG) to protect from unblinding the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Data collected during the double-blind treatment period will be summarized by intervention group and, where appropriate and applicable, compared between intervention groups with hypothesis tests.

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

9.1. Statistical Hypotheses

The primary hypothesis of this study is that selexipag reduces risk of disease progression compared to placebo in pediatric participants with PAH.

9.2. Analysis Timepoints

CCI [redacted] the 4 planned analyses are as specified in Section 4.1. Additional information is provided below:

Analysis 1 CCI [redacted] when at least 80 participants have been treated and followed up for at least 24 weeks in the double-blind treatment period. Participants who prematurely discontinued the study in the double-blind treatment period prior to 24 weeks will also be included in the analysis.

Analysis 1 will be performed by an unblinded CCI [redacted] team CCI [redacted] before completion of the double-blind treatment period (see Section 6.3). The study team remains blinded to this analysis.

Analysis 2 is CCI [redacted] with a data cutoff date when approximately 125 participants have been followed up for at least 24 weeks or prematurely discontinued the study in the double-blind treatment period.

The study team will be unblinded after database lock for Analysis 2. Site personnel and participants will remain blinded until the announcement of the end of the double-blind treatment period.

Analysis 3 is CCI [redacted] at the end of the double-blind treatment period after all participants included in Analysis 2 have completed their EOT visit. Site personnel and participants will be unblinded.

Analysis 4 is the analysis of the OLEP after all participants have completed the 3-year OLEP or have prematurely discontinued the study.

9.3. Sample Size Determination

For the CCI [redacted] (Analysis 1), the sample size is not based on formal statistical considerations.

CCI [redacted]

CCI

Table 4: CCI

CCI

9.4. Populations for Analyses

For analysis purposes, the following populations are defined:

Table 5: Overview of the Different Populations for Analyses

Population	Description
Screened Analysis Set (SCR)	All participants who were screened and received a participant identification number.
Full Analysis Set (FAS)	All participants assigned to a study intervention.
Per-Protocol Analysis Set (PPS)	All participants who received the assigned study intervention and who complied with the protocol sufficiently to be likely to exhibit the intervention effects.
Safety Analysis Set (SAS)	All participants who received at least one dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK Analysis Set (PKAS)	All participants in FAS with at least one evaluable trough PK concentration
Quality of Life Set (QoLS)	All participants in FAS enrolled in a country/territory participating in QoL
Selexipag-Initiated Set (SIS)	All participants initiated at any time during DB or OL intervention on selexipag.

DB = double-blind; OL = open-label; PK = pharmacokinetics.

Table 5 defines all analysis sets. For Analyses 1, 2 and 3, time to disease progression up to EOT the primary endpoint, will be evaluated on the FAS. The same analysis set will be used for the evaluation of other efficacy endpoints. Safety endpoints will be primarily evaluated on the SAS. The SIS will be used for Analysis 4 to evaluate participants initiated at any time on selexipag.

9.5. Statistical Analyses

9.5.1. Primary Efficacy Analysis

Variable

Time from randomization to first occurrence of CEC-confirmed disease progression up to 7 days after study intervention discontinuation. Disease progression is a composite endpoint (including death due to any cause) and is defined in Section 3.

Participants who do not experience any disease progression while on treatment will have their time to disease progression right-censored at the time of study intervention discontinuation +7 days.

Time to first disease progression will be expressed in days and calculated as the onset date of the first CEC-confirmed disease progression event minus date of randomization +1 or, for censored participants, as censoring date minus date of randomization +1.

Main Analysis

Analysis 1 and Analysis 3:

The analysis will be performed on participants in the FAS, according to the randomized treatment group.

Time to disease progression will be descriptively summarized with Kaplan-Meier estimates and 95% confidence intervals for probability of no event for each treatment group and displayed in both a graphical and a tabular form. In addition, the number of participants at risk, the number of participants censored and the number of participants with event will be computed at each time point for each treatment group.

Analysis 2:

The analysis will be performed on participants in the FAS, according to the randomized treatment group.

In addition to the descriptive analysis specified above for Analysis 1 and 3, an exploratory analysis for the between-treatment comparison will be performed using Cox proportional hazards model, including treatment group, WHO FC (II vs III) at baseline and PAH-specific treatment at baseline (monotherapy vs combination therapy) as explanatory variables. The resulting selexipag/placebo hazard ratio and 95% confidence interval will be presented.

9.5.2. Secondary Efficacy Analysis

9.5.2.1. CCI [redacted]

Variable

Change in CCI [redacted] from baseline to Week 24 will be expressed as $\log_2$(Week 24/Baseline).

Main Analysis

Analysis 1

CCI [redacted] in $\log_2$(Week 24/Baseline) will be summarized with geometric mean and its 95% confidence interval for each treatment group.

Analysis 2

CCI [redacted] in $\log_2$(Week 24/Baseline) will be analyzed using analysis of covariance (ANCOVA), including treatment group, $\log_2$(baseline CCI [redacted] WHO FC (II vs III) at baseline and PAH-specific treatment at baseline (monotherapy vs combination therapy) as explanatory variables. The geometric mean and its 95% confidence interval of each treatment group will be presented. Between-treatment geometric mean ratio and its 95% confidence interval will also be presented.

Analysis 3

Not applicable.

Supplementary analysis for Analysis 2

CCI

The CCI responder rate will be analyzed using logistic regression analysis, including treatment group, WHO FC (II vs III) at baseline, PAH-specific treatment at baseline (monotherapy vs combination therapy), age, sex, and renal function (if there are at least 20% participants with impaired renal function) as explanatory variables.

9.5.2.2. Time to First CEC-confirmed Hospitalization for PAH or Death Due to PAH

Variable

Time from randomization to first occurrence of CEC-confirmed hospitalization for PAH or death due to PAH up to 7 days after study treatment discontinuation.

Participants who do not experience any event while on treatment will have their time right-censored at the time of study treatment discontinuation +7 days.

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

Main Analysis

Same approaches as for the primary efficacy endpoint (Section 9.5.1).

9.5.3. Safety Analyses

Adverse Events

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

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

Summaries for the double-blind treatment period will be by study intervention (selexipag or placebo) and will include all events up to the start of the open-label period, or up to 30 days after study intervention discontinuation, whichever occurs first.

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

Clinical Laboratory Tests

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

Vital Signs

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

Growth

Change from baseline in growth variables (BMI, height and weight) will be summarized at each scheduled time point by intervention group.

In addition, body weight (kg) and body length/height (cm) will be plotted over time as individual curves per participant. The x-axis will display age in months. The y-axis will display the growth variable of interest, weight (kg) or length/height (cm). Separate figures will be created for male and female participants, with overlays of sex-specific standard WHO growth percentiles by age for the 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles. All collected values of weight and length/height will be used.

A different symbol will be used for each treatment group.

Sexual maturation

Sexual maturation changes from baseline as measured by the Tanner stage will be summarized at each scheduled time point by intervention group.

9.6. Other Analyses

Other exploratory endpoints, as well as the OLEP endpoints, will be summarized with descriptive statistics by intervention group. Details will be specified in SAPs.

Pharmacokinetic Analyses

Trough plasma concentration at steady-state, $C_{trough,ss}$, will be listed and summarized by dose and body-weight cohort, with arithmetic mean, geometric mean, minimum, median, maximum, standard deviation, standard error, coefficient of variation in %, and 95% CI of the arithmetic and geometric means.

If considered appropriate, plasma concentration of selexipag and its active metabolite ACT-333679 may be analyzed using population PK analysis. The PK data of this study may be combined with those of other selected studies to support relevant nonlinear mixed effects modeling. Details of the population PK analysis (including potential snapshot dates, treatment for

missing or below limit of quantification observations, criteria for exclusion, PK parameters and descriptive statistics to be estimated, etc) will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Quality of Life Analyses

Changes from Baseline in QoL scores will be analyzed over time by means of a repeated measures mixed model on values at each visit (including baseline) in the QoLS. The model will include randomized treatment, visit, treatment by visit interaction, the randomization stratification factor and baseline value as fixed effects, while participant will be included as a random effect.

Adjusted least squares means within each treatment group and adjusted estimates of the differences in change from baseline between treatment groups will be displayed for each visit along with their corresponding 2-sided 95% CIs.

Plots of QoL variables profiles over time will be provided.

9.7. Interim Analysis

There are no inferential interim analyses for any efficacy endpoint.

CCI

[redacted]

9.8. Independent Data Monitoring Committee

An IDMC will be established as noted in Committees Structure in Section 10.4.

The IDMC has the overall responsibility for safeguarding the interests of participants by monitoring safety data obtained in the study and by making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC will be fully operational prior to the enrollment of the first participant in the study. The composition and operation of the IDMC is described in the IDMC charter.

Detailed information on the IDMC is available in Section 10.4, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

(e)CRF	Case report form(s) (paper or electronic as appropriate for this study)
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
aPAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
ASO	Arteriosclerosis
ASO-IC	Arteriosclerosis obliterans-intermittent claudication
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve over 24 hours
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve over one dosing interval at steady-state
$AUC_{\tau,ss\ ACT\text{-}333679}$	Area under the plasma concentration-time curve of ACT-333679 over one dosing interval at steady-state
$AUC_{\tau,ss,\ selexipag}$	Area under the plasma concentration-time curve of selexipag over one dosing interval at steady-state
$AUC_{\tau,ss,combined}$	Combined exposure over one dosing interval at steady-state
AxMP	Auxiliary Medicinal Product
BCAC	Baseline Characteristics Adjudication Committee
Bid	Twice daily
BP	Blood pressure
BREATHE	Bosentan Randomized trial of Endothelin Antagonist THErapy for pulmonary hypertension
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Confidence limit
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum concentration at steady-state
CP	Conditional power
CRO	Contract research organization
CTEPH	Chronic thromboembolic pulmonary hypertension
$C_{trough,ss}$	Trough plasma concentration at steady-state
CYP	Cytochrome P450
DBP	Diastolic blood pressure
EARLY	Endothelin antagonist trial in mildly symptomatic PAH patients
ECG	Electrocardiogram
eCOA	Eectronic clinical outcome assessment
eDC	electronic data capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EP_4	Prostaglandin-E2 subtype 4
ERA	Endothelin receptor antagonist
ET	Endothelin
ET-1	Endothelin-1

EU	European Union
FAS	Full Analysis Set
FC	Functional class
FDA	Food and Drug Administration
FUTURE	Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion
GCIS	Global Clinical Impression Scale
GCP	Good Clinical Practice
GRIPHON	Prostacyclin (PGI2G) receptor agonist in Pulmonary arterial HypertensiON
GSD	Group-sequential design
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
IC	Intermittent claudication
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
iMTD	Individual maximum tolerated dose
IMP	Investigational Medicinal Product
INR	International Normalized Ration
IP	Prostacyclin receptor
iPAH	Idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board
ISSG	Independent, unblinded statistical support group
Iv	Intravenous(ly)
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan-Meier
LAR	Legally authorized representative
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary arterial pressure
NT-proBNP	N-terminal pro-brain natriuretic peptide
OLEP	Open-label extension period
PAH	Pulmonary arterial hypertension
PAH-aCTD	Pulmonary arterial hypertension associated with connective tissue disease
PAWP	Pulmonary arterial wedge pressure
PDE-5	Phosphodiesterase type-5
PGI2	Prostacyclin
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Se
PPS	Per-Protocol Analysis Set
PTA	Post-trial access
PQC	Product Quality Complaint
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
PVRi	Pulmonary vascular resistance index
QoL	Quality of Life
QoLS	Quality of Life Set
RBC	Red blood cell

RHC	Right heart catheterization
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBP	Systolic blood pressure
SCR	Screened Analysis Set
SIS	Selexipag-Initiated Set
SmPC	Summary of Product Characteristics
SSc	Systemic sclerosis
SUSAR	Suspected unexpected serious adverse reaction
Tid	Three times a day
T_{max}	Time to reach C_{max}
TOMORROW	pediaTric use Of Macitentan tO delay disease pRogRessiOn in PAH Worldwide
TOPP	Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension
TSH	Thyroid-stimulating hormone
UGT	Uridine 5’-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
USPI	United States Prescribing Information
WHO	World Health Organization

10.2. Appendix 2: Anticipated Events

No anticipated events are defined for this study.

10.3. Appendix 3: Clinical Laboratory Tests

A central laboratory (refer to 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 participant, 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 (with corresponding normal ranges) include hospitalization of the participant due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If 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.

All laboratory reports must be reviewed, signed and dated by the investigator or delegate and filed with the source documents. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of 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 (refer to Section 8.4 and Appendix 4).

The participants 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 central laboratory manual.

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF.

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	White Blood Cell count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A white blood cell evaluation may include any abnormal cells, which will then be reported by the laboratory. A red blood cell (RBC) evaluation may include abnormalities in the RBC count, RBC parameters (eg, mean corpuscular volume [MCV])], or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported. Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN [>35% direct bilirubin]) reporting requirements are defined in Section 8.6.1	
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose [no fasting requirement] Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyltransferase	Total & Direct bilirubin Alkaline phosphatase Calcium Albumin Cholesterol Creatinine clearance NT-proBNP TSH Thyroid antibodies (Antithyroglobulin & Thyroperoxidase antibody) Free T3 and free T4 Uric acid
Other Tests	For female participants of childbearing potential: • Screening: Serum Pregnancy Testing • Randomization/Day 1 & every 4 weeks (± 3 days) thereafter up to 30 days after EOT: Urine pregnancy tests. • Serum pregnancy testing every 4 weeks (± 7 days) for participants on study treatment with bosentan after PAH disease progression. Results of the urine pregnancy tests performed after Day 1 are recorded on a mobile electronic device (eDiary) by the participant. Compliance with urine pregnancy testing every 4 weeks (± 3 days) is monitored by the investigator and not collected in the CRF. Participants on bosentan provided as rescue medication require a serum pregnancy test prior to treatment initiation with bosentan and monthly during treatment with bosentan. Last pregnancy test must be performed 30 days after last study intervention (placebo/selexipag) and treatment with bosentan, if applicable.	

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the participants).

- Investigator's Brochure (or equivalent information) and amendments/addenda.
- Sponsor-approved participant recruiting materials.
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- Investigator's *curriculum vitae* or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

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

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

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

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

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

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

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

INFORMED CONSENT PROCESS AND ASSENT FORM

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by Health Authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally

acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent/assent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 42 days from the previous ICF signature date.

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

Participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. Assent must be obtained from participants who are able to write. A separate assent form in language the participant can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the participant, and to the participant's parent(s) or if applicable legally acceptable representative.

DATA PROTECTION

Privacy of Personal Data

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

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

The informed consent/assent obtained from the participant (or his or her legally acceptable representative) includes information about, and where required per applicable regulations, explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring,

audit, IEC/IRB review, and regulatory inspection. This informed consent/assent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

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

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

COMMITTEES STRUCTURE

Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis, to review interim data, and to ensure the continuing safety of the participants enrolled in this study. This committee will consist of at least one medical expert in pediatric PAH and at least one statistician. Committee membership, responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

Clinical Event Committee

A CEC consisting of independent PAH experts including pediatricians will be appointed to adjudicate primary endpoint events of the study in a blinded fashion (refer to Section 8.2.1.3). Committee membership, responsibilities, authorities, and procedures are documented in its charter. In the presence of disease progression (elements of the primary endpoint as defined in Section 3), a patient dossier will be compiled and provided to the CEC for review.

Generic/brand names of PAH-specific medications will be blinded to the CEC to reduce assessment bias. If there is any change to key data (defined in the CEC charter) or new key data become available after a first submission of a participant case to the CEC, the CEC coordinator re-submits the case for re-adjudication.

The CEC coordinator will provide feedback on the adjudication decisions to the investigators.

Baseline Characteristics Adjudication Committee (BCAC)

A BCAC will review and approve the randomization of participants with PAH with coincidental CHD, ie, small atrial septal defect, ventricular septal defect or patent ductus arteriosus which themselves do not account for the development of elevated PVR (coincidental CHD). Committee membership, responsibilities, authorities, and procedures will be documented in its charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent/assent.

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will

be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, electronic transfer of clinical laboratory data from a central laboratory, actigraphy, imaging into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

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

CASE REPORT FORM COMPLETION

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

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

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into

CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

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

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

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

SOURCE DOCUMENTS

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

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

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

Entries recorded through a mobile electronic device by the participant/parents/LAR(s) in the patient-reported outcomes and by the investigator (refer to Sections 8.4 and 8.5), and electronically transferred clinical laboratory data, and imaging data (echocardiography) are considered source data.

Study intervention intake data recorded by the participant/LAR(s) on a mobile electronic device (refer to Section 6.4) are reviewed by the investigator to advise the participant/LAR(s) on study intervention compliance and complete the study intervention log in the CRF. These data are considered source data and will not be transferred to the CRF.

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

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

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

MONITORING

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

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

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

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

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

ON-SITE AUDITS

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

for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

RECORD RETENTION

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

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

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

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study/Site Termination

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

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

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

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

10.5. Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.6.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Study-site staff should instruct caregivers (parent/LAR) on how to report signs and symptoms (eg, crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc). These non-specific symptoms may be the only manifestations of some adverse reaction observed in toddlers. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Moreover, symptoms that are dependent on participant communication ability (eg, nausea, pain, mood alterations) in younger or mentally disabled children could potentially be at risk for under- or mis-reporting.

Serious Adverse Events

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important*.

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

All events of aminotransferase ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event, the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For selexipag, the expectedness of an AE will be determined by whether or not it is listed in the Reference Safety Information section provided in the Investigator's Brochure.

For study rescue therapy with bosentan, the expectedness of an AE will be determined by whether or not it is listed in the Tracleer EU SmPC which will be the reference safety information document for this assessment.

10.5.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

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

Not Related

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

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.5.3. Severity Criteria

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

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

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

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

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

10.5.4. Special Reporting Situations

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

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

Participant-specific special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF and reported on SAE Form.

10.5.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF (refer to Section 8.6). Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study intervention. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

Refer to Section 8.6 for more information on the reporting procedures of SAEs.

All SAEs that have not resolved at time of the EOS visit (refer to Section 8.6) must be followed until any of the following occurs:

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

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

The follow-up information obtained after the participant's EOS visit (refer to Section 4.4) must be reported to the sponsor but will not be recorded in the eCRF.

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE.

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

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).

- Surgery or procedure planned before entry into the study (must be documented in the source notes) or hospitalization for standard monitoring or investigation of a pre-existing disease or medical condition that did not worsen. Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. However, any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered an SAE.

10.5.6. Product Quality Complaint Handling

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

Procedures

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

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

10.5.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.6. Appendix 6: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.6.4, Pregnancy and Section 10.5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

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

The methods of birth control used (only pharmacological methods) and, if applicable, the reason for not being of childbearing potential must be recorded in the eCRF.

Definitions

Female of Childbearing Potential (FOCBP)

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (refer to below).

Female Not of Childbearing Potential

- **premenarchal**
  - A premenarchal state is one in which menarche has not yet occurred.
- **permanently sterile**
  - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

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

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
• Oral or injectable contraceptive agents, implants or transdermal contraceptive hormone
• Intrauterine device (IUD)
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
• Diaphragm; female condom or cervical cap; or partner's use of a condom, and any of these used in combination with a spermicide.
For participants receiving bosentan study treatment[a]: • Estrogen and progesterone oral contraceptives ("the pill"), OR • Estrogen and progesterone transdermal patch, OR • Vaginal ring, OR • Progesterone injection, OR • Progesterone implant, **AND** • Male Condom
a) Hormonal contraception may be susceptible to interaction with the bosentan study treatment, which may reduce the efficacy of the contraceptive method. Male condom and female condom should not be used together (due to risk of failure with friction).

Contraceptive and Barrier Guidance for participants receiving bosentan

For participants receiving bosentan after PAH-progression as described in Section 10.16, hormone-based contraceptives alone, including oral, injectable, transdermal or implantable forms, are not considered as reliable methods of contraception. Due to PK interactions, bosentan may render hormonal contraceptives ineffective. Therefore, females of childbearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception (please refer to the table above for participants receiving bosentan study treatment). If there is any doubt about what contraceptive advice should be given to the individual participant, consultation with a specialist/gynecologist is recommended.

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 4, 8 April 2022:

The main reason for the current amendment is the addition of different mini-tablet dose strengths: 100 µg mini-tablets and 150 µg mini-tablets for participants in the body-weight categories ≥9 to <25 kg and ≥25 to <50 kg, respectively. Minor corrections and editorial revisions are also being implemented. A Protocol Amendment Summary of Changes Table for the current amendment is provided below.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis Endpoints; 3 Objectives and Endpoints	Updated text under exploratory endpoints pertaining to time to disease progression for clarification.	To clarify the text pertaining to time to disease progression for better readability.
1.1 Synopsis Endpoints; 3 Objectives and Endpoints	Updated frequency of acceptability assessment from "Day 1" to "Week 4" for consistency with earlier updates.	To modify for consistency with earlier updates as it is not possible to have the acceptability assessment on Day 1 at site, when the first dose is only taken in the evening, likely after leaving the site.
1.1 Synopsis Overall Design; 4.1 Overall Design; 9.2 Analyses; 9.2.1 Analysis 1; 9.2.2 Analysis 2; 9.2.3 Analysis 3	Updated the analysis time periods for Analysis 1 and Analysis 2 from "at the end of CCI [redacted]" Also, updated the analysis time period for Analysis 3 from "at the end of CCI [redacted]"	To allow operational flexibility in line with Health Authority agreement on study closure.
1.1 Synopsis Intervention Groups and Duration	Updated text to clarify study intervention supply with bottles of 200 µg tablets as well as 50 µg mini-tablets of selexipag and matching placebo will be supplied by the sponsor.	To align with the text from Section 6.1 Study Intervention Administered for consistency.
1.1 Synopsis Intervention Groups and Duration; 6.1 Study Interventions Administered	Added information on 2 mini-tablets dosage strengths (100 µg and 150 µg) introduced for participants in the body-weight categories ≥9 to <25 kg and ≥25 to <50 kg.	To reduce the number of tablets to be taken and to ease the dispersion in apple and orange juice.
1.2 Schema	Updated the Figure 1 and footnote to include definition of abbreviations used in the figure.	To revise for adding definitions of abbreviations used in the figure.
1.3.1 Visit and Assessments Schedule During Double-blind Treatment Period until Week 12; 8.2.5 Physical Activity/Accelerometry	Updated footnote and text to explain time periods to collect data for accelerometry at any time between Visit 1 and Visit 2 and during the 10 to 14 consecutive days before respective visits (Visit 5/Week 12).	To clarify time periods to collect data for accelerometry.

Section Number and Name	Description of Change	Brief Rationale
1.3.2 Visits and Assessments After Week 12 - for Participants Continuing Double-blind Study Drug Treatment until End of Study	Updated footnote "s" to clarify frequency of Tanner stage assessment for participants continuing double-blind study drug treatment.	To clarify the frequency of Tanner stage assessments.
1.3.2 Visits and Assessments After Week 12 - for Participants Continuing Double-blind Study Drug Treatment until End of Study; 1.3.3 Visits and Assessments after EOT - for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study; 1.3.4 Visits and Assessments During the Open-Label Extension Period; 10.3 Appendix 3: Clinical Laboratory Tests; 10.16.12 Safety Assessments	Updated footnote to clarify frequency of serum pregnancy tests in female participants of childbearing potential from "monthly" to "every 4 weeks ± 3 days."	To clarify the frequency of serum pregnancy test assessments in female participants of childbearing potential.
1.3.2 Visits and Assessments After Week 12 - for Participants Continuing Double-blind Study Drug Treatment until End of Study; 1.3.3 Visits and Assessments after EOT - for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study; 1.3.4 Visits and Assessments During the Open-Label Extension Period; 5.1 Inclusion Criteria #7; 8.3.5 Childbearing Potential; 10.3 Appendix 3: Clinical Laboratory Tests	Updated frequency of urine pregnancy tests in female participants of childbearing potential from "monthly" to "every 4 weeks ± 3 days."	To clarify the frequency of urine pregnancy test assessments in female participants of childbearing potential.

Section Number and Name	Description of Change	Brief Rationale
1.3.3 Visits and Assessments after EOT - for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study	Deleted text from the table pertaining to serum pregnancy test "or serum for participants on bosentan study treatment" as it is covered under hematology and chemistry and for consistency with other tables.	To modify for consistency with other instances used in the protocol.
4.1 Overall Design	Added definitions of abbreviations CEC and EMA to the Figure 2 footnote.	To modify for adding definitions of abbreviations used in the figure.
5.1 Inclusion Criteria #6	Modified inclusion criterion #6 to clarify inclusion of participants who are receiving a stable dose with at least 1 PAH-specific treatment for at least 3 months prior to "first dose of study intervention," which was at least 3 months prior to "screening" earlier.	To clarify schedule of assessing inclusion criterion for participants receiving PAH-specific treatment.
5.1 Inclusion Criteria #7; 10.6 Appendix 6: Contraceptive and Barrier Guidance; 10.16.12 Safety Assessments	Updated information on contraceptive barrier methods that are not considered highly effective. Revised text from "a highly effective method" to "an effective method."	To align with the contraceptive methods provided in the appendix, which include barrier methods that are generally not considered "highly" effective.
5.2 Exclusion Criteria #5	Modified information in exclusion criterion #5 to clarify that participants with history of bronchopulmonary dysplasia are excluded.	To clarify the exclusion criterion to exclude participants with history of bronchopulmonary dysplasia.
5.2 Exclusion Criteria #23	Modified exclusion criterion #23 to clarify exclusion of participants who have cerebrovascular events within the last 3 months prior to "first dose of study intervention," which was mentioned as "within the last 3 months prior to enrollment" earlier.	To clarify schedule of assessing exclusion criterion cerebrovascular events.
6.1 Study Interventions Administered; 7.2 Participant Discontinuation	Updated text to clarify study intervention interruption of 3 days corresponds to 6 consecutive scheduled study intervention administrations.	To clarify study intervention interruption details per teams' recommendation.
6.1 Study Interventions Administered	Added text to clarify that selexipag or matching placebo will be considered as Investigational Medicinal Product (IMP).	To implement requirement related to the European Clinical Trial Regulation including the classification of treatment related to the study as IMP, Auxiliary Medicinal Product (AxMP), and Concomitant Therapy. Accordingly, double-blind study intervention (selexipag/placebo) is classified as IMP.

Section Number and Name	Description of Change	Brief Rationale
6.1 Study Interventions Administered; 10.16.5 Study Intervention Administered	Added and updated text to clarify that optional treatment with bosentan following CEC-confirmed disease progression will be considered as an Auxiliary Medicinal Product (AxMP).	To implement requirement related to the European Clinical Trial Regulation including the classification of treatment related to the study as IMP, AxMP, and Concomitant Therapy. Accordingly, bosentan rescue treatment is classified as AxMP.
6.5 Concomitant Therapy	Updated text to clarify that PAH-specific standard of care will be considered as a concomitant therapy.	To implement requirement related to the European Clinical Trial Regulation including the classification of treatment related to the study as IMP, AxMP, and Concomitant Therapy. Accordingly, PAH-specific standard treatments are classified as concomitant therapy.
7.1 Discontinuation of Study Intervention	Updated reference citation for text related to hyperthyroidism. Replaced Uptravi® SmPC and Uptravi® USPI references citation with selexipag Investigator's Brochure.	To revise reference citation to align with the latest update available.
8.3.3 Electrocardiogram	Clarified that the order of assessments of ECG(s), vital signs, blood draw is recommended and not mandatory.	For consistency with the introduction of Section 8, which recommends the order of assessments.
8.6.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Updated the text regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor "immediately, but no later than 24 hours," which was "within 24 hours" earlier.	To align with latest protocol template language.
9.4 Operating Characteristics of the Selected Design	Updated text from "-Hwang-1990, with ShiDeCani 1990" to "Hwang-Shi-DeCani 1990" to be consistent with the other occurrences in the protocol.	To modify for consistency with other instances used in the protocol.
10.1 Appendix 1: Abbreviations and Trademarks	Added abbreviations AxMP and IMP and their definitions to the list of abbreviations.	To align with the new information added in the protocol.
10.3. Appendix 3: Clinical Laboratory Tests	Added the text from the latest template "The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF."	To align with latest protocol template language.
10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations; Informed Consent Process and Assent Form	Deleted text pertaining to "written" informed consent.	To align with latest protocol template language.

Section Number and Name	Description of Change	Brief Rationale
10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations; Data protection	Updated text pertaining to informed consent.	To align with latest protocol template language.
10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations; Study and Site Closure	Updated the title of the subsection from 'Study Termination" to "Study/Site Termination."	To align with latest protocol template language.
8.6.1 Serious Adverse Events; 10.3 Appendix 3: Clinical Laboratory Tests; 10.5.1. Adverse Event Definitions and Classifications	Added text "All events of aminotransferase ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE."	To modify for consistency with other instances used in the protocol.
10.5.4. Special Reporting Situations	Added a bullet: • Reporting of participant pregnancy or participant partner pregnancies.	To align with the requirements in Section 8.6.4 and with the latest protocol template language.
10.6 Appendix 6: Contraceptive and Barrier Guidance	Updated the definition of permanently sterile (for the purpose of this study), to include "Has congenital abnormalities resulting in sterility."	To align with the latest protocol template language.
10.6 Appendix 6: Contraceptive and Barrier Guidance	Revised text on examples of contraceptives used for participants receiving bosentan study intervention.	To adjust acceptable methods of contraception to be in line with the bosentan label based on different local availabilities of spermicides.
10.11 Appendix 11: Child-Pugh Classification	Added additional reference levels with different units for total bilirubin (µmol/L) and serum albumin (g/L) to assess the severity of liver disease per Child-Pugh classification.	To align with the central laboratory units.
Guidance on Study Conduct During A Natural Disaster/Major Disruption/Pandemic (EDMS-RIM-263730, 4.0)	Updated the Corona Virus Disease 2019 (COVID-19) Appendix title and content to include natural disasters and major disruptions.	To provide guidance for conducting the study under special circumstances not only related to COVID-19 but also to natural disasters, major disruptions, and pandemics.
10.16.10 Discontinuation of Treatment with Bosentan	Updated in-text citation for cross-referring Section 10.6, which was earlier Section 6.	To provide correct in-text citation for cross-referring the section.

Section Number and Name	Description of Change	Brief Rationale
11 References	Combined 2 references selexipag Investigator's Brochure and selexipag Investigator's Brochure Amendment 1 as the new version for selexipag Investigator's Brochure is available. Updated Edition number and Year for selexipag Investigator's Brochure citation from Edition 14, 2019 to Edition 17, 2022. Updated references Uptravi® SmPC and Uptravi® USPI to align with the updated versions available. The in-text reference citation was also updated in the applicable sections of the protocol.	To align with the new versions available.
11 References	Deleted reference "ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7" from the references as the language pertaining to the reference was deleted in earlier versions.	To align with the body of the protocol.
Throughout the protocol	Updated the terms "country" and "countries" to "country/territory" and "countries/territories," respectively in the body of the protocol per updated template. Minor grammatical, formatting, or spelling changes were made.	To align with the latest protocol template language. Minor errors were corrected.

Amendment 3, 20 May 2021:

The main reasons for the current amendment are to update the recently approved study intervention administration options, to clarify testing strategy of primary and secondary efficacy endpoints per FDA's advice (Lechmacher 1999 method has been described for the frequentist approach) and to implement other minor corrections. A Protocol Amendment Summary of Changes Table for the current amendment is provided below.

Section Number and Name	Description of Change	Brief Rationale
1.3.1. Visit and Assessment Schedule During Double-blind Treatment Period Uptitration Period Until Week 12	Window period is added on Day 1 in case of overnight 2-day randomization. Footnote "d" of "1 week is equal to 7 days" is added for better clarification. Window period of ±3 days added in footnote "l" for serum pregnancy test.	To accommodate overnight 2-day randomization for participants living far away from study site; for logistical reasons. Footnote added for better clarification. To allow flexibility in serum pregnancy test conduct window period is added.
1.3.2. Visits and Assessments After Week 12 - for	Window period of ±3 days added.	To update missing details from previous version.

Participants Continuing Double-blind Study Drug Treatment until End of Study		
1.3.3. Visits and Assessments after EOT - for Participants Discontinuing Double-blind Study Drug Treatment Before End of Study; 4.1. Overall Design; 7.1. Discontinuation of Study Intervention	Number of days updated from 7 days to 10 days after last study drug dose for End of double-blind treatment.	To allow more flexibility for patients living further away from the site.
1.3.4. Visits and Assessments During the Open-Label Extension Period	Window period of ±3 days is added for open label- individual maximum tolerated dose (OL-iMTD) visit at Week 12.	For consistency with the main study uptitration window for Week 12.
5.2. Exclusion Criteria	Exclusion criterion 29 is deleted.	Exclusion criterion is no more applicable due to updated option of study intervention administration.
6.1. Study Intervention Administered	• Options for study intervention supply are revised to include recently approved option of study intervention administration: 'dispersed in apple/orange juice.' • Study intervention administration instructions are updated. • Information about study site personnel's function to instruct the study participants, parents and LAR to capture the study intervention administration in an eDiary is updated.	To update additional approved option of study intervention administration, based on CMC study outcomes. Instruction related to study intervention administration is updated. The study intervention is allowed to be administered with beverages like apple or orange- juice is also updated. Thus, the wordings are updated accordingly. To provide appropriate guidance for data capture in eDiary and study intervention storage.
8.1.3 Baseline Disease Characteristics and Baseline Narrative	Following sentence related to baseline narrative is updated: 'The Baseline narratives will be provided to the Sponsor for overview of document completeness and to CEC for assessing a potential primary endpoint event in case of disease progression.'	Review of the baseline narratives by the sponsor is added for better overview of the completeness of these documents.
9.6.1 Primary Efficacy Analysis [Strategy 2: Main Analysis (frequentist)]	Strategy 2: Main Analysis (frequentist) subsection is updated by adding clarifications following the FDA advice letter. Supporting reference (Lehmacher 1999) is cited and included in list of references.	To clarify testing strategy of primary and secondary efficacy endpoints per FDA's advice (Lehmacher 1999 method has been described for the frequentist approach).
9.6.2. Secondary Efficacy Analysis	Main Analysis (frequentist)-related wordings are added for secondary efficacy variable.	
10.3. Appendix 3: Clinical Laboratory Tests (Other Tests)	Information about urine and serum pregnancy test to be conducted at particular	To align with JNJ safety reporting processes.

	timepoints for female participants of childbearing potential that are sexually active during and after treatment with study intervention (placebo/selexipag) or bosentan is updated.	
10.5.1. Adverse Event Definitions and Classifications (Unlisted [Unexpected] Adverse Event/Reference Safety Information)	Following information is updated: 'For study rescue therapy with bosentan, the expectedness of an AE will be determined by whether or not it is listed in the Tracleer EU SmPC which will be the reference safety information document for this assessment.'	
Throughout the document	The term 'subject' and 'patient' replaced with 'participant' wherever applicable. The term 'caregiver' was redefined as 'parent or legally acceptable representative (LAR).' Study intervention containing 50 μg of selexipag is referred as 'mini-tablet'. Additional minor corrections and clarifications were made.	For consistency. Minor errors were noted.
COVID-19 Appendix (EDMS-RIM-263730, 3.0)	Standalone COVID-19 appendix is updated	COVID-19 appendix is updated with standard text finalized by Janssen.

Amendment 2, 13 October 2020:

The main reasons for the current amendment are to update the recently approved study intervention administration options, to clarify testing strategy of primary and secondary efficacy endpoints per FDA's advice (Lechmacher 1999 method has been described for the frequentist approach) and to implement other minor corrections. A Protocol Amendment Summary of Changes Table for the current amendment is provided below.

Section Number and Name	Description of Change	Brief Rationale
Title Page, 8.2.6 6-Minute Walk Distance	Introduction of the study name SALTO	Logistical update.
1.1 Synopsis, 2.3 Benefit/Risk Assessment, 4.1 Overall Design	Addition of the pharmacokinetic (PK) interim analysis report as background for the study treatment starting doses in age cohort 2.	Selexipag starting doses confirmation from the AC-065A203 study.
5.2 Exclusion Criteria	Addition of a reference to the appendix defining the Child-Pugh score.	Logistical update.
6 Study Intervention and Concomitant Therapy, 6.7 Treatment of Overdose	Update of the title of the section and addition of Section 6.7 Treatment of overdose	Added additional information on the treatment of overdose. In addition, the section "Treatment of overdose" was moved from Section 8.7 to Section 6.
6.2.Preparation/Handling/Storage/Accountability	Study intervention storage conditions were updated.	To consistently refer to the label for the appropriate study

		intervention storage conditions.
7.1 Discontinuation of Study Intervention	Updated the information about discontinuation of study intervention	To resolve a contradiction to Section 1.3.3, according to which the end of treatment (EOT) visit has to occur within 7 days of treatment discontinuation.
8. Study Assessments and Procedures	Updated references to the serious adverse event (SAE), pregnancy-notification and follow-up forms. Addition of the Product Quality Complaint (PQC) form.	To adapt to updated internal processes.
10.6 Appendix 6: Contraceptive and Barrier Guidance	The names of the SAE and pregnancy notification forms were updated.	To adapt to updated internal processes.
8.6 Adverse Events and Serious Adverse Events	The title of this section was updated to "Adverse Events, Serious Adverse Events, and Other Safety Reporting." Reference to "disease related events" was removed. The separate SAE fax cover page is no longer required, it is now part of the SAE Form.	To adapt to updated internal processes.
8.6.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Addition of PQC to the safety reporting process. General updates related to the safety reporting process.	To adapt to updated internal processes.
8.6.2 Follow-up of Adverse Events and Serious Adverse Events	Updated information regarding the follow-up of adverse events (AEs).	To adapt to updated internal processes.
8.6.3 Regulatory Reporting Requirements for Serious Adverse Events	Updated information regarding blinded suspected unexpected serious adverse reactions (SUSAR) summaries.	To adapt to updated internal processes.
8.6.4 Pregnancy	Addition of requirement for pregnancy reporting in female partners of male study participants.	To adapt to updated internal processes.
8.6.5 Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events	Reference to disease related events was removed.	To adapt to updated internal processes.
8.7 Treatment of Overdose	The section on treatment of overdose has been clarified and moved to Section 6.7 Subsections in Section 6 and 8 are also renumbered.	To adapt to updated internal processes.
8 Study Assessments and Procedures	References to "Actelion" were replaced by reference to "Sponsor."	To adapt to updated internal processes.
10.5 Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions	The title of this section was updated to "Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and	To adapt to updated internal processes.

and Procedures for Recording, Evaluating, Follow-up, and Reporting	Procedures for Recording, Evaluating, Follow-up, and Reporting." Updated definitions of Unlisted (Unexpected) AEs.	
10.5.2 Attribution Definitions	Updated definitions for the assessment of causality of AEs.	To adapt to updated internal processes.
10.5.6 Product Quality Complaint Handling	Updated guidance on the handling of product quality complaints.	To adapt to updated internal processes.
10.5.7 Contacting the Sponsor Regarding Safety, Including Product Quality	Section 10.5.7 is new, the information was previously included in Section 10.5 and replaced.	To adapt to updated internal processes.
10.6 Appendix 6: Contraceptive and Barrier Guidance	The title of this section was updated and instructions on pregnancy reporting and follow-up were removed (they are covered in Section 8.6).	To adapt to updated internal processes.
10.11 Appendix 11: Child-Pugh Classification	Correction of the scoring of prothrombin time (PT) and addition of international normalized ratio (INR) for a score = 1 from >4 seconds to <4 seconds. Corresponding references have been cited.	To provide additional guidance depending on which laboratory assessment is performed and correction of a typographical error
10.16.6 Appendix 16: Treatment with Bosentan after CEC-confirmed PAH-progression (Preparation/Handling/Storage/ Accountability)	Bosentan storage conditions were updated.	To consistently refer to the label for the appropriate study intervention storage conditions.
10.16.12 Safety Assessments	Added the text: All events of aminotransferase ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.	To adapt to updated internal processes.
10.1 Appendix 1: Abbreviations and Trademarks	The Abbreviations list and Definition of Terms were updated	Not applicable
11 References	List of references updated.	To align with JNJ style guide.
Throughout the Protocol	Titles of Section 8.6, 10.5, and 10.6 are updated throughout.	To adapt to updated internal processes.
Throughout the protocol	Minor editorial and document formatting revisions.	Not applicable

COVID-19 Appendix (EDMS-RIM-263730, 2.0) (03 August 2020)

The COVID-19 appendix was introduced to provide guidance for study conduct during the COVID-19 pandemic.

Amendment 1, 06 March 2020:

The main reasons for the current amendment are to update the recently approved study intervention administration options, to clarify testing strategy of primary and secondary efficacy endpoints per FDA's advice (Lechmacher 1999 method has been described for the frequentist approach) and to

implement other minor corrections. A Protocol Amendment Summary of Changes Table for the current amendment is provided below.

Section Number and Name	Description of Change	Brief Rationale
1.2 Schema	Moving the first palatability and acceptability assessment from Visit 2/Day 1 to Visit 3/Week 4.	As the first dose of the new study intervention must be taken in the evening of Day 1. the palatability/acceptability assessment is moved to Visit 3/Week 4.
1.2 Schema	The schematic overview of the study was updated for clarity and minor corrections included.	The schematic overview erroneously indicated that CEC-confirmed disease progression would require end of treatment. In addition, analysis timepoints were removed from the schema, since they are explained more comprehensively in the synopsis and in the body of the protocol.
2.3 Benefit/Risk Assessment **4.1 Overall Design**	Addition of updated dosing information from AC-065A203. The dosing recommendation has been confirmed for patients in age cohorts 1 and 2. Thus, enrolment into the age cohort 2 (≥6 to <12 years of age) can be initiated.	This information was added following interim analysis 2 of AC-065A203.
4.1 Overall Design	The group sequential designs for strategy 2 was updated. In particular, the primary analysis is frequentist with an overall type I error at 4% 1-sided. Clarity is added to the description of the analysis timepoints for the 2 strategies and a figure is added to better illustrate the complexity of the statistical analyses.	The description of the group sequential design for strategy 2 was updated in consideration of HA feedback. In addition, was amended for clarity.
5.2 Exclusion criteria	Added exclusion criterion 29.	To ensure potential participants unable to swallow tablets with water or soft food are excluded.
5.2 Exclusion criteria	It was clarified for exclusion criterion 16 that Child-Pugh scoring is required in potential participants with hepatic impairment.	Clarification.
5.4 Screen Failures	Corrected that screen-failures receive a new participant number in case of re-screening	Correction.
6.1 Study Interventions Administered	In addition to swallowing study treatment whole with water, swallowing mini-tablets with soft food (mashed banana, yogurt, apple sauce/puree/mousse) is permitted. In addition, a treatment supply option of providing 50 µg tablets only (as opposed to a combination of 50 µg and 200 µg tablets has been introduced for participants in the body-weight category ≥ 9 to < 25 kg.	Swallowing study intervention with soft food aims at providing a more convenient method of administration, in particular for young participants. This is supported by photostability data. To additionally ease study treatment administration, investigators can choose to provide patients in the ≥ 9 to < 25 kg body-weight group with 50 mg mini-tablets only.

Section Number and Name	Description of Change	Brief Rationale
7.1 Treatment discontinuation	Further clarified that if a subject develops hepatic impairment a Child-Pugh Scoring needs to be done and fully documented.	Clarification.
8.2.5 Physical Activity/Accelerometry	The physical activity/accelerometry details were updated to indicate that wear compliance is monitored and that investigators will have access to accelerometry raw data for filing purposes.	This information was missing previously.
8.3.4 Tanner stage	The ages at which Tanner stage needs to be assessed in boys and girls were clarified.	Clarification.
9.2 Analyses, 9.3 Sample Size Determination	The group sequential strategy for strategy 2 was updated consistently with section 4.1. The informative Bayesian rescue strategy is dropped from the primary analysis. Specifically, the primary analysis is frequentist with an overall type I error at 4% 1-sided and the number of events for the group sequential design (used for information fraction) is set to 109. The maximum for SSR is changed from 145 to 125 events. Operating characteristics for strategy 2 are updated accordingly.	The informative Bayesian strategy as a rescue for primary analysis is removed in consideration of different requirements from Health Authorities. The number of events used as maximum information fraction in the GSD is set to 109, accounting for the target treatment effect of HR=0.60, overall type I error at 4% 1-sided and the number of events needed to achieve 80% given the planned interim analyses features. The maximum number of events for SSR at 125 corresponds to the number events CCI [redacted] according to current protocol assumptions.
10.3 Appendix 3: Clinical Laboratory Tests	The units for all laboratory parameters were removed in the table "Protocol-Required Safety Laboratory Assessments"	The units are no longer to be specified with implementation of the Janssen standard units.
10.5 Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	An instruction was added that sites staff needs to instruct parents/legal representatives to report specific and non-specific symptoms in small children in particular.	This addition aims at ensuring appropriate AE reporting in participants who can't verbalize specific symptoms.
10.6 Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	The definitions of acceptable methods of contraception were updated	The methods of acceptable contraception erroneously did not include barrier methods. The use of barrier methods is allowed per the selexipag label(s) and was therefore also included as an option.
10.8 Appendix 8: Guidelines for 6MWD Test	Deleted from the protocol and will be a separate document	Aligned across Actelion studies
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.
Synopsis	The synopsis was updated according to the changes described above.	

10.8. Appendix 8: WHO Functional Class

WHO functional class

Class I Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

10.9. Appendix 9: Panama Functional Class for Pediatrics

For children aged 2–5 years

Class I Asymptomatic, growing normally, attending nursery/school regularly, no limitation of physical activity, playing sports with his/her classmates.

Class II Slight limitation of physical activity, unduly dyspneic and fatigued when playing with his/her classmates. Comfortable at rest. Continues to grow along own centiles. Nursery/school attendance 75% normal. No chest pain.

Class IIIa Marked limitation of physical activity. Regression of learned physical activities. Not climbing stairs, reluctant to play with friends. Hesitant and unadventurous. Comfortable at rest. Less than ordinary activity (eg, dressing) causes undue dyspnea, fatigue, syncope and/or presyncope, or chest pain. Nursery/schooling compromised < 50% normal attendance.

Class IIIb Unable to attend nursery/school, but mobile at home. Wheelchair needed outside home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue, syncope or chest pain. Plus features of Class IIIa.

Class IV Unable to carry out any physical activity without undue dyspnea, fatigue, syncope, or chest pain, unable to attend school, wheelchair dependent, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III.

For children aged 5–16 years

Class I Asymptomatic, growing along own centiles, attending school regularly, no limitation of physical activity, playing sports with his/her classmates.

Class II Slight limitation of physical activity, unduly dyspneic and fatigued when playing with his/her classmates. Comfortable at rest. Continues to grow along own centiles. School attendance 75% normal. No chest pain.

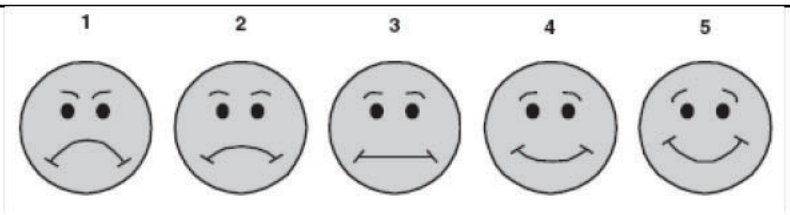
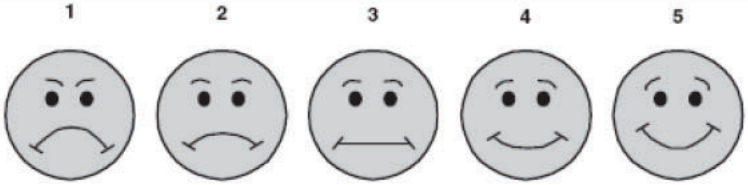
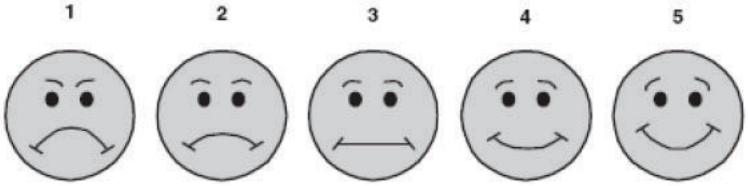
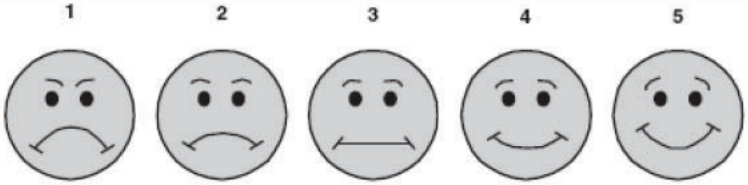
Class IIIa Marked limitation of physical activity. No attempt at sports. Comfortable at rest. Less than ordinary activity causes undue dyspnea, fatigue, syncope, or chest pain. Schooling compromised < 50% normal attendance.

Class IIIb Unable to attend school, but mobile at home and interacting with friends. Wheelchair needed outside the home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity (eg, dressing) causes undue dyspnea, fatigue, syncope and/or presyncope, or chest pain. Plus features of Class IIIa.

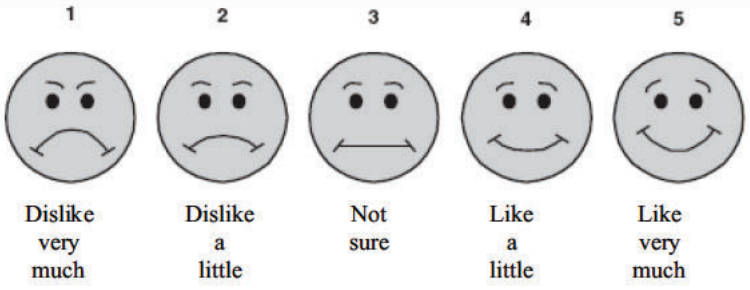
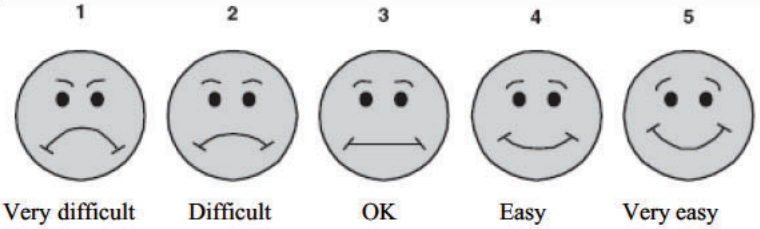
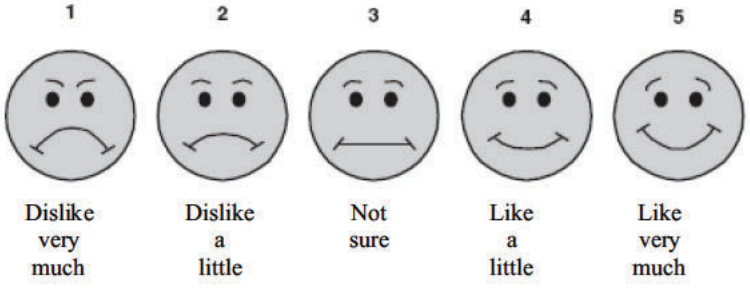
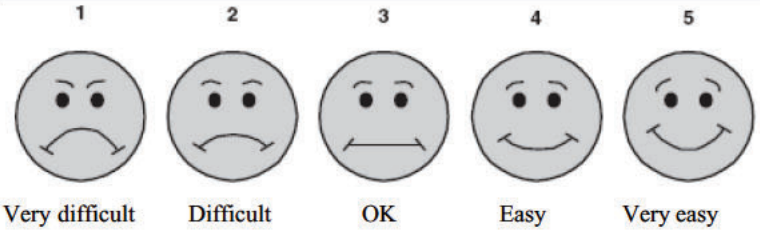
Class IV Unable to carry out any physical activity without undue dyspnea, fatigue, syncope, or chest pain, unable to attend school, wheelchair dependent, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III.

10.10. Appendix 10: Palatability and Acceptability of Study Intervention

PALATABILITY QUESTIONNAIRE FOR PARTICIPANTS

1.	How much do you like the taste of this medicine?	
2.	How easily can you swallow this medicine?	
3.	How much do you like that this medicine is taken twice every day?	
4.	How easy is it to remove the medicine from the packaging?	

PALATABILITY QUESTIONNAIRE FOR CAREGIVERS/SITE PERSONNEL

1.	On the basis of reaction/facial expression of your child, how much do you believe your child likes the taste of this medicine?	
2.	On the basis of reaction/facial expression of your child, how easily can your child swallow this medicine?	
3.	How much do you like that this medicine is given twice every day?	
4.	How easy is it to remove the medicine from the packaging?	

10.11. Appendix 11: Child-Pugh Classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to Table 6 (adapted from FDA 2003 and Vincent 2012):

Table 6: Child-Pugh Classification

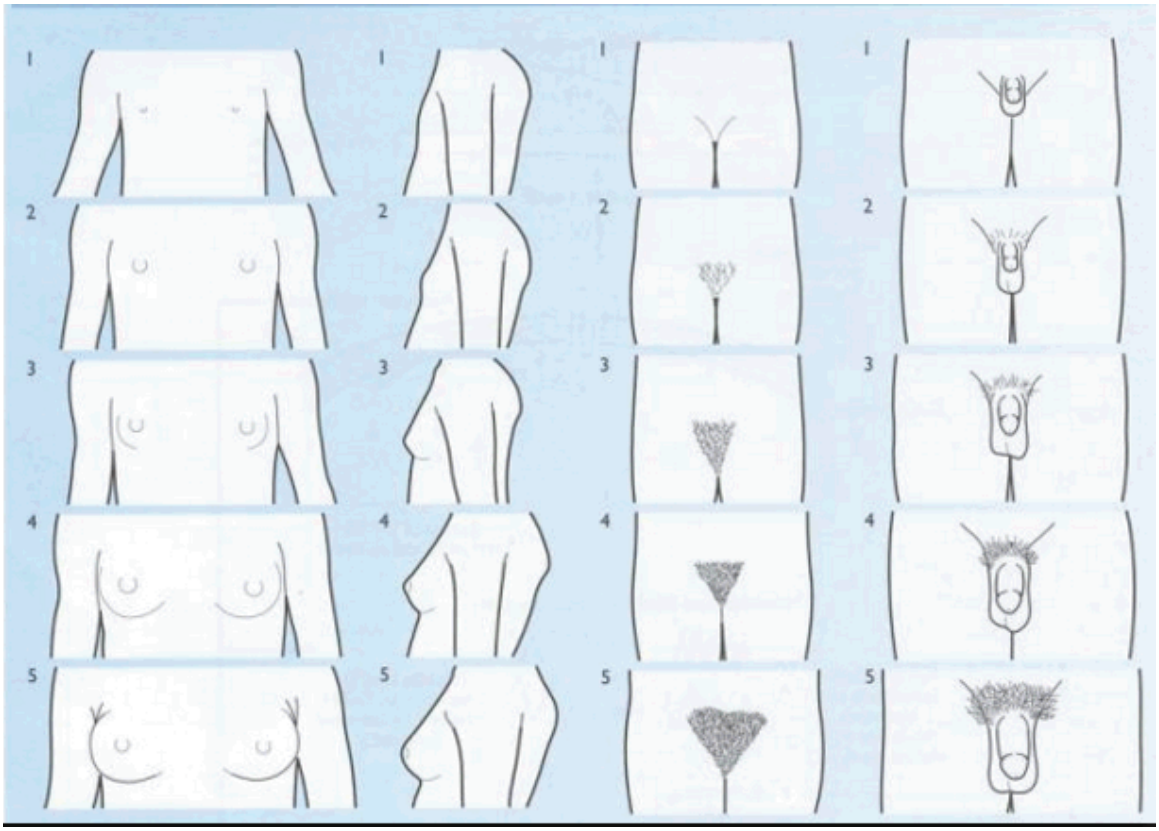
	Score		
	1	**2**	**3**
Total bilirubin			
mg/dL	<2.0	2.0-3.0	>3.0
µmol/L	<34	34-51	>51
Serum albumin			
g/dL	>3.5	2.8-3.5	<2.8
g/L	>35	28-35	<28
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy*	Grade 0	Grade 1-2	Grade 3-4
Prothrombin time (seconds or	<4	4-6	>6
INR	<1.7	1.7 – 2.2	>2.2

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, 5 cycles per second waves.
• Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
• Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
• Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cycles per second delta activity.

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

10.12. Appendix 12: Tanner Scale



Illustrated by Michal Komorniczak (Poland)

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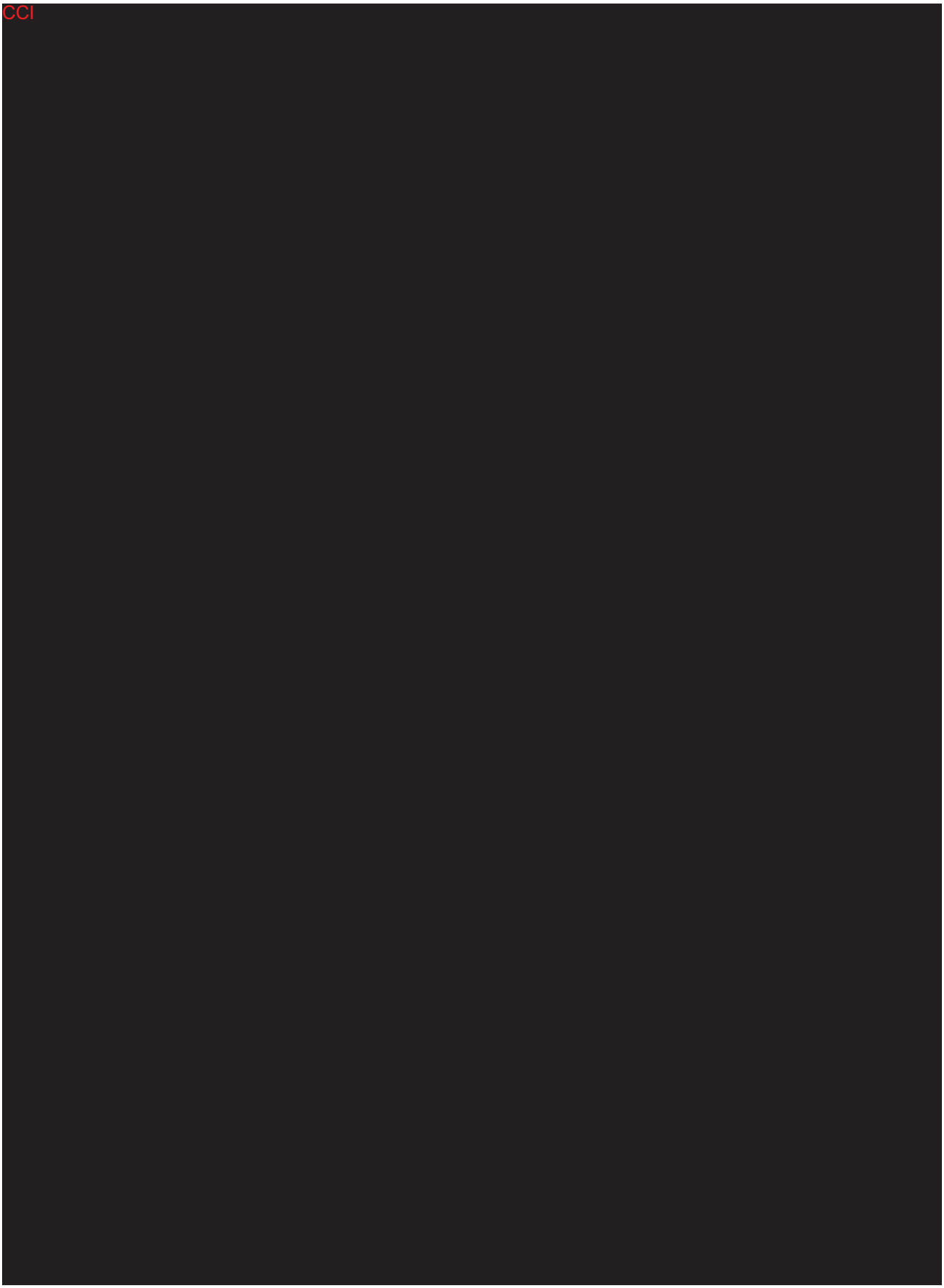

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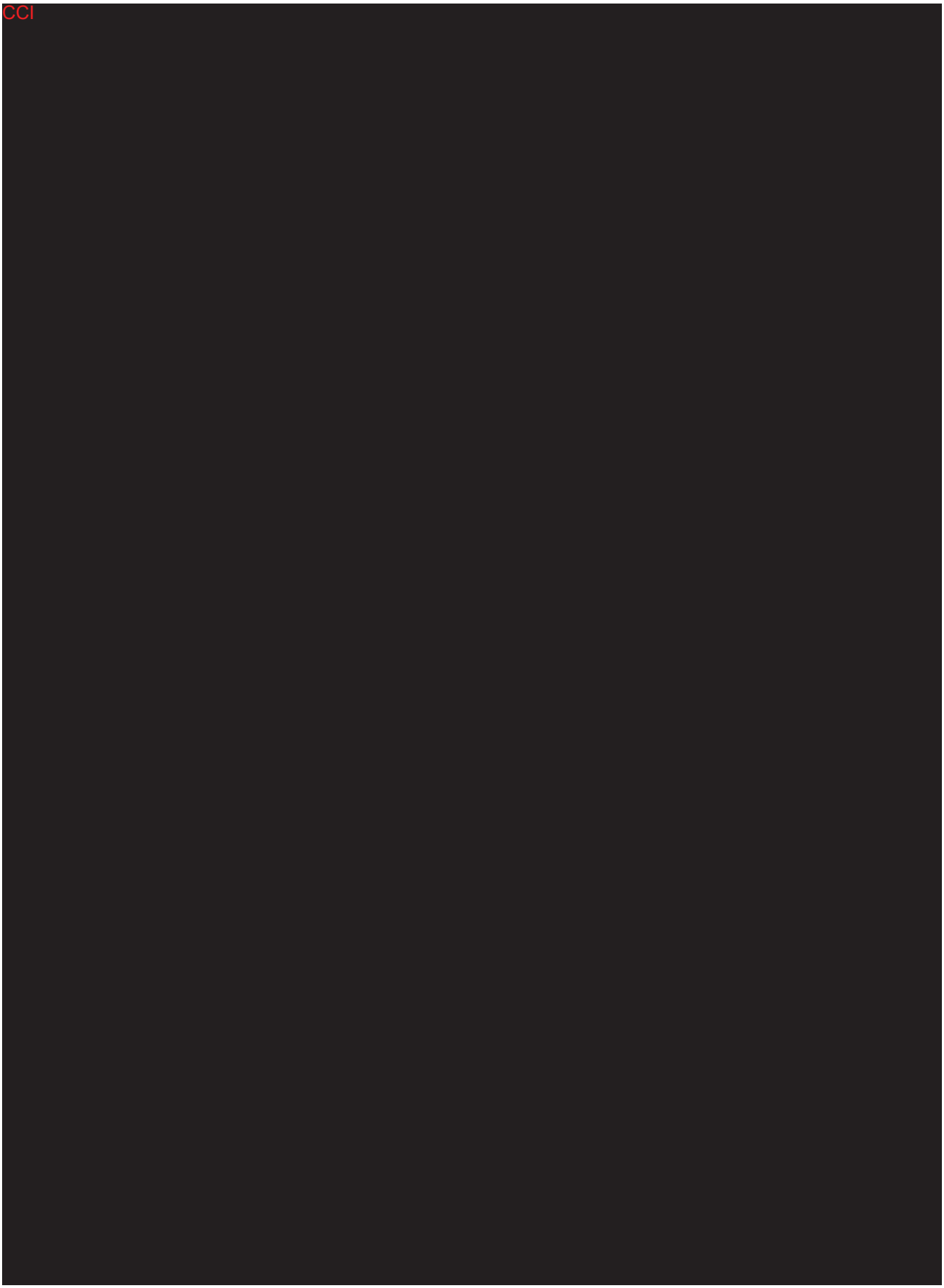

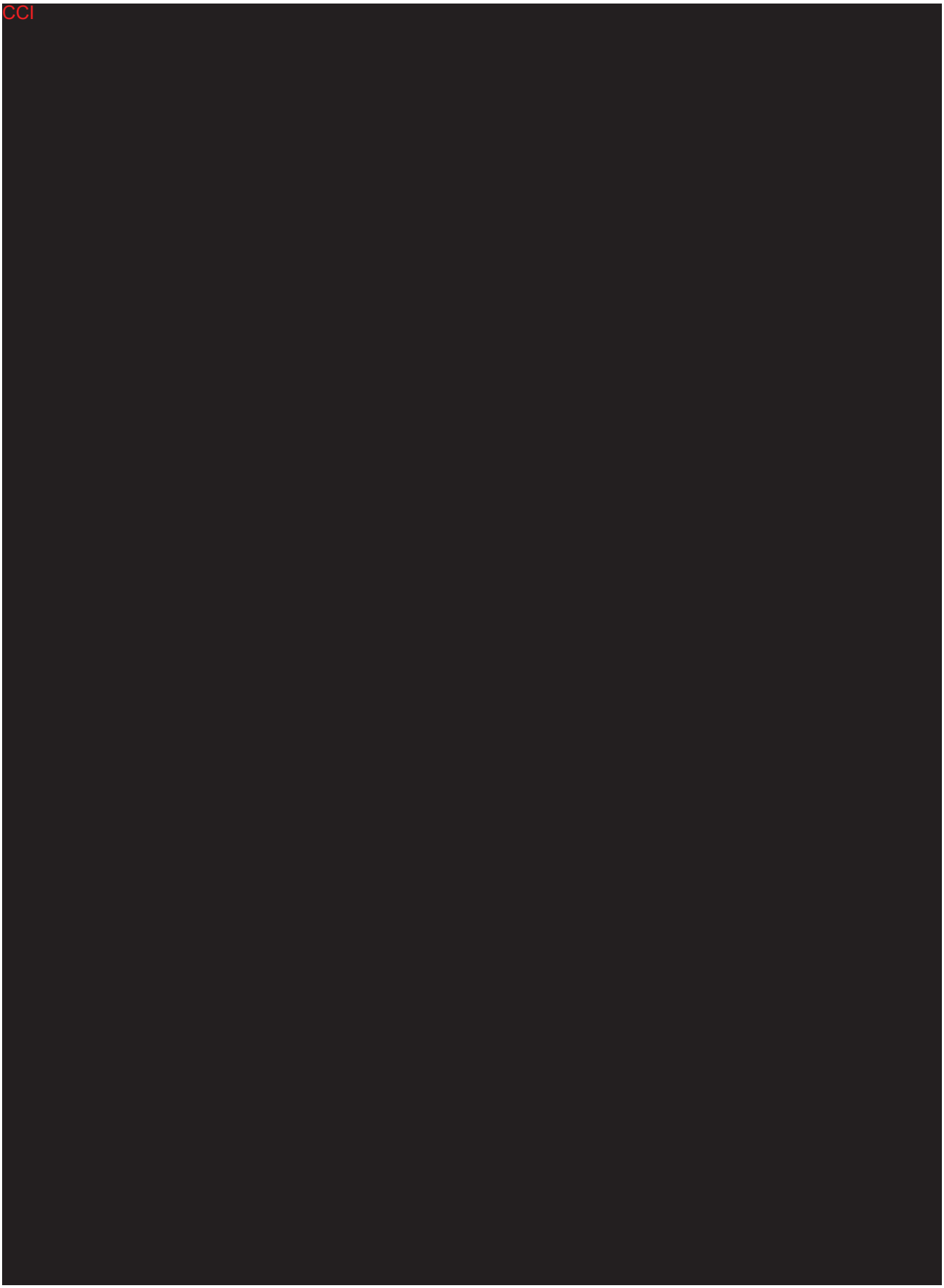
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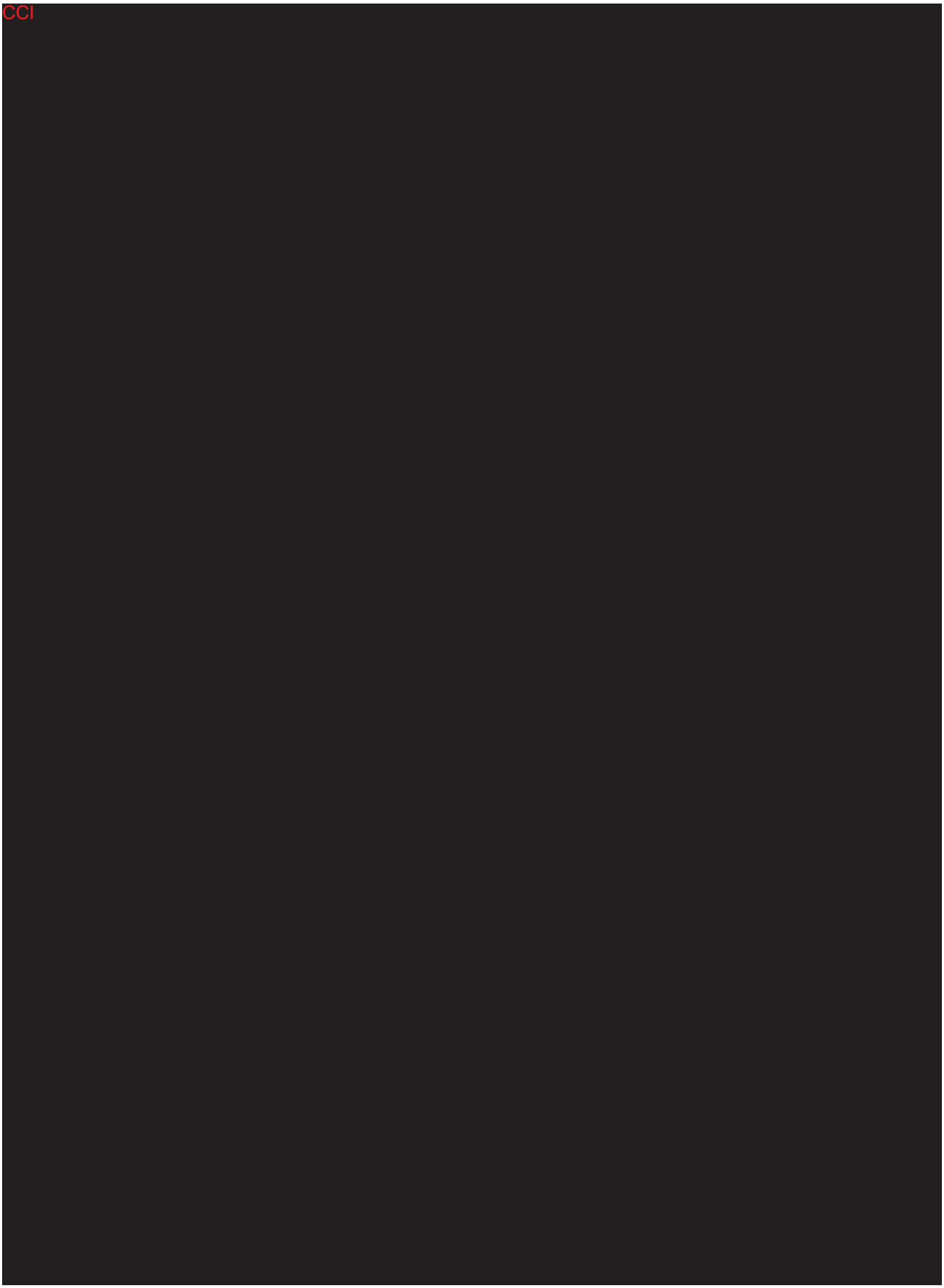

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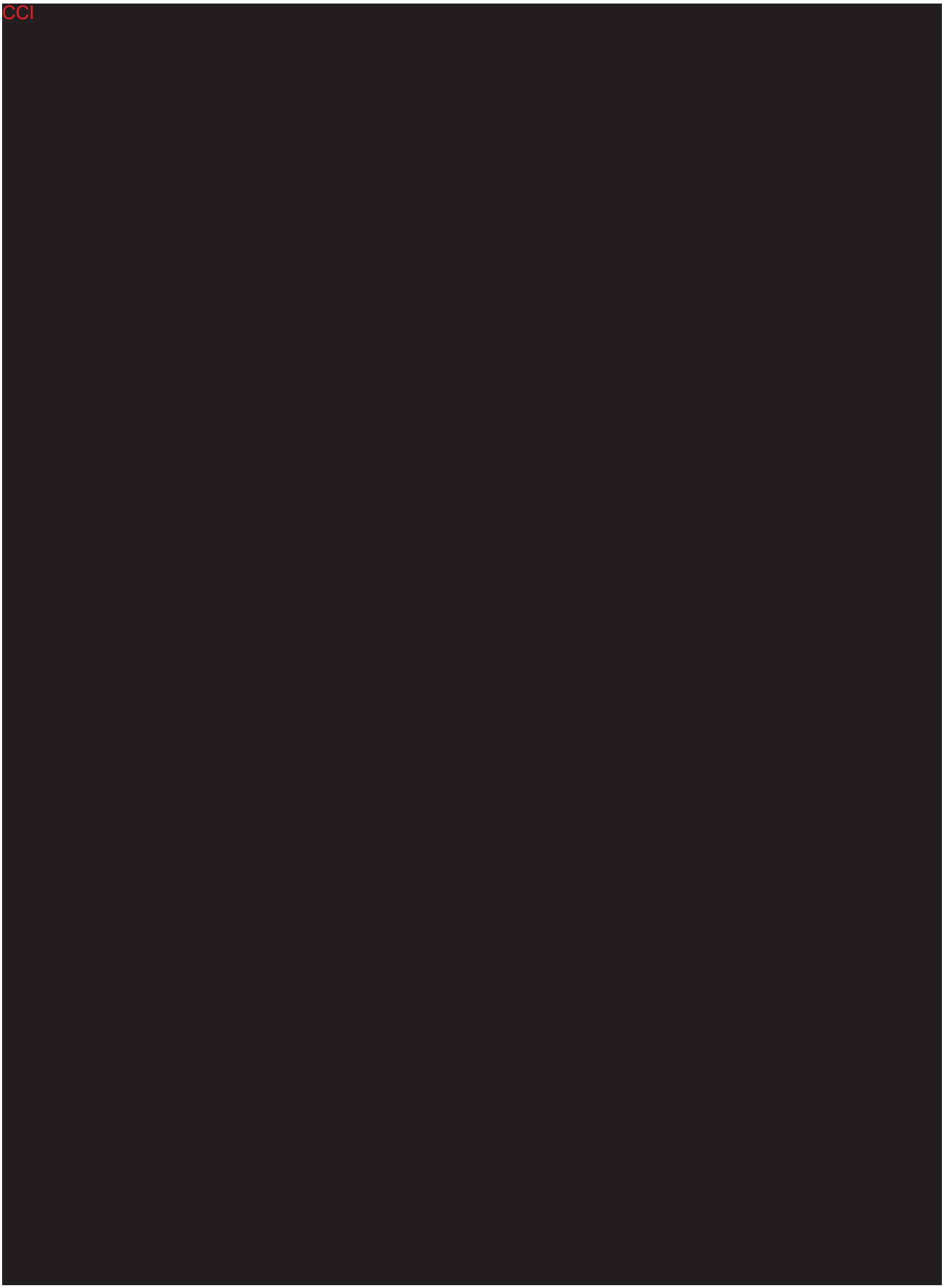

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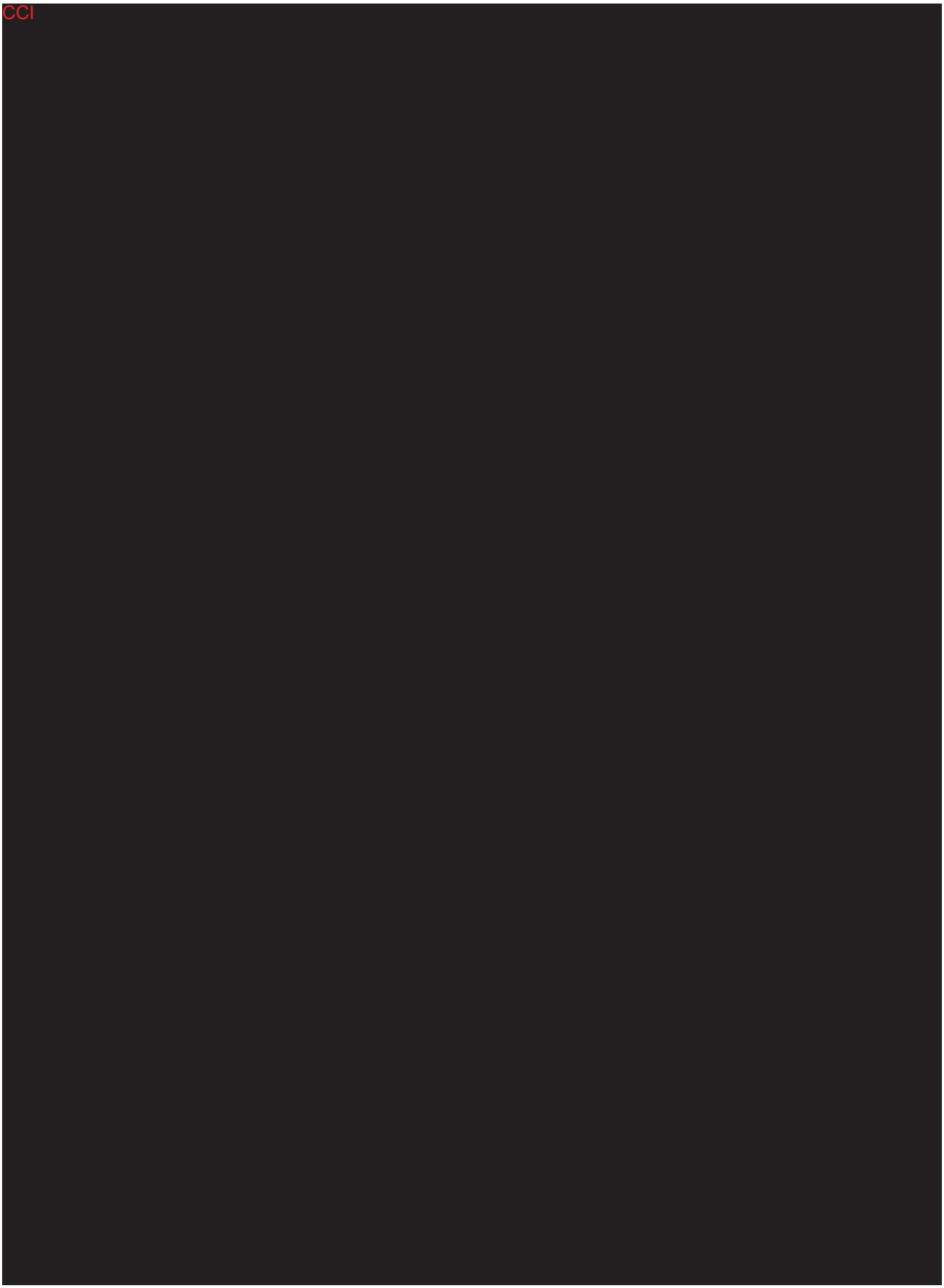

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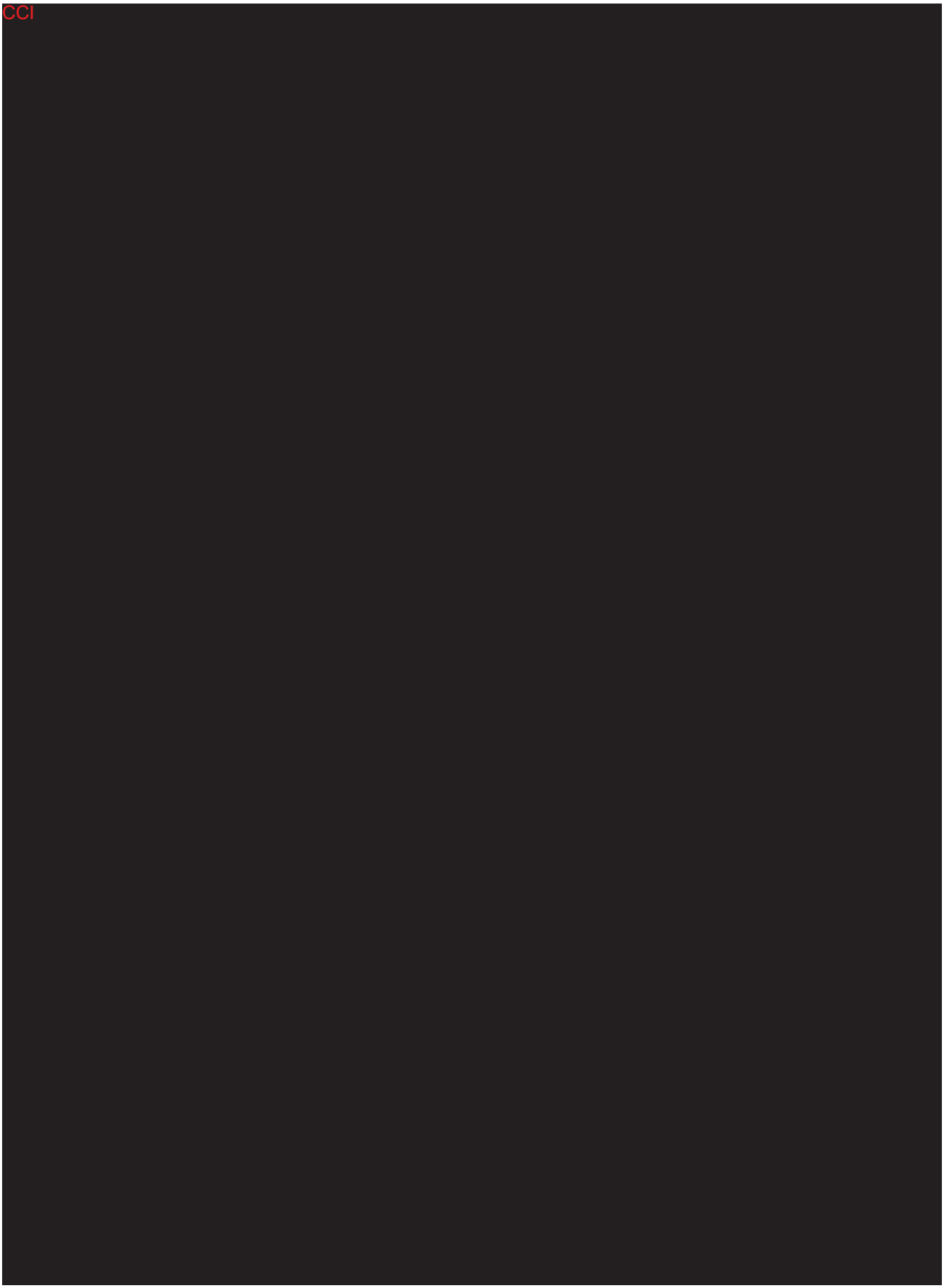

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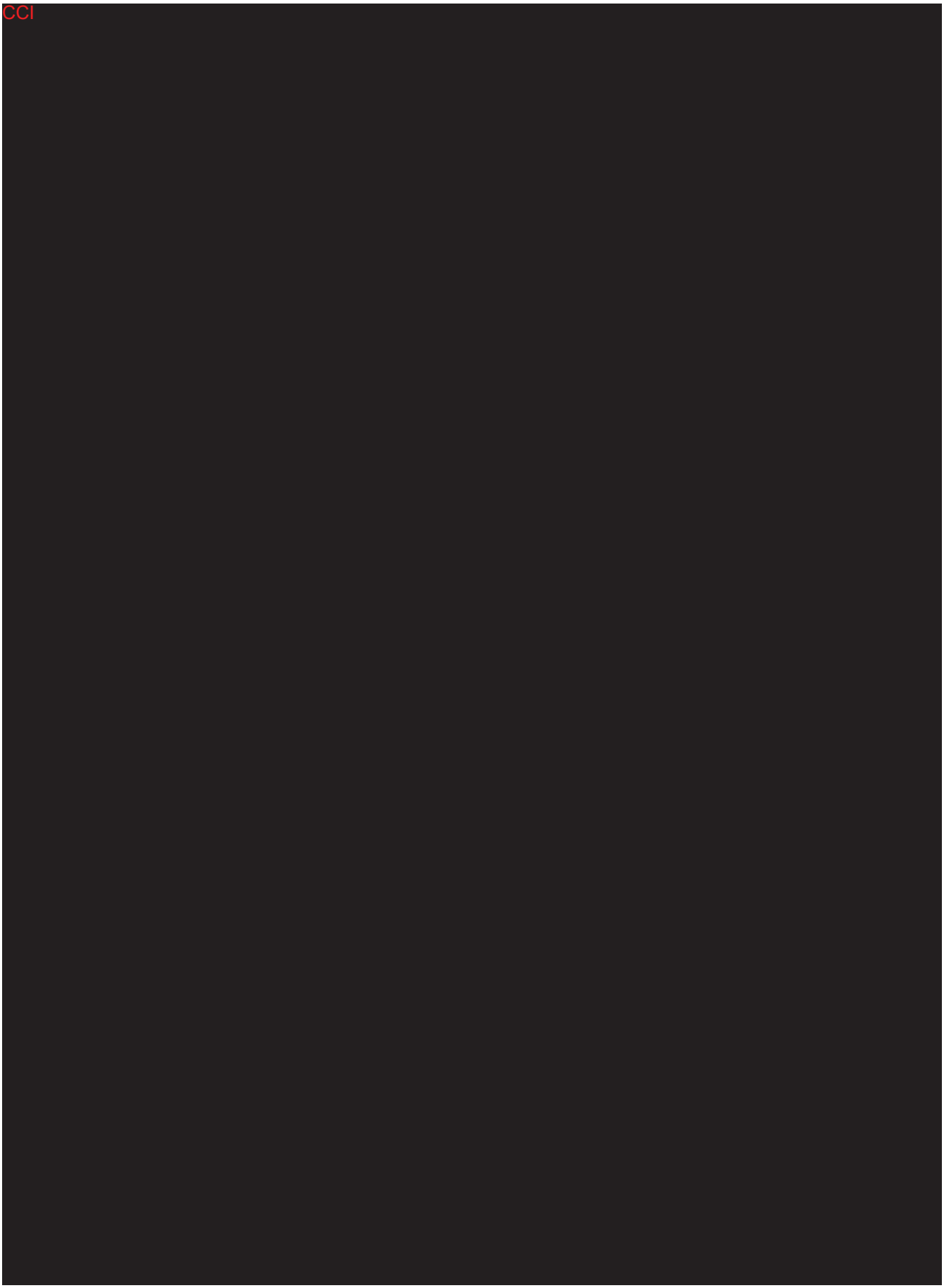

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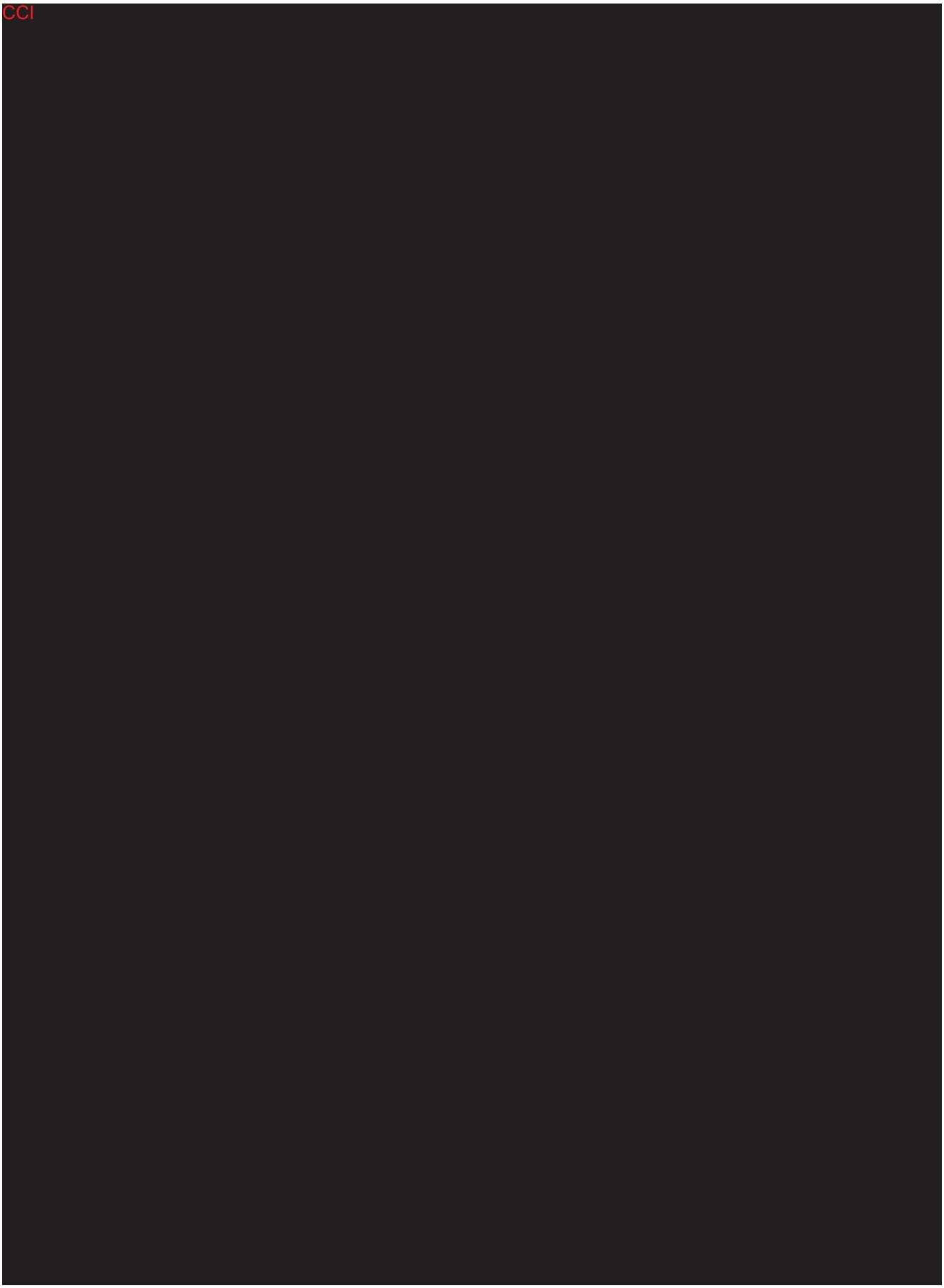

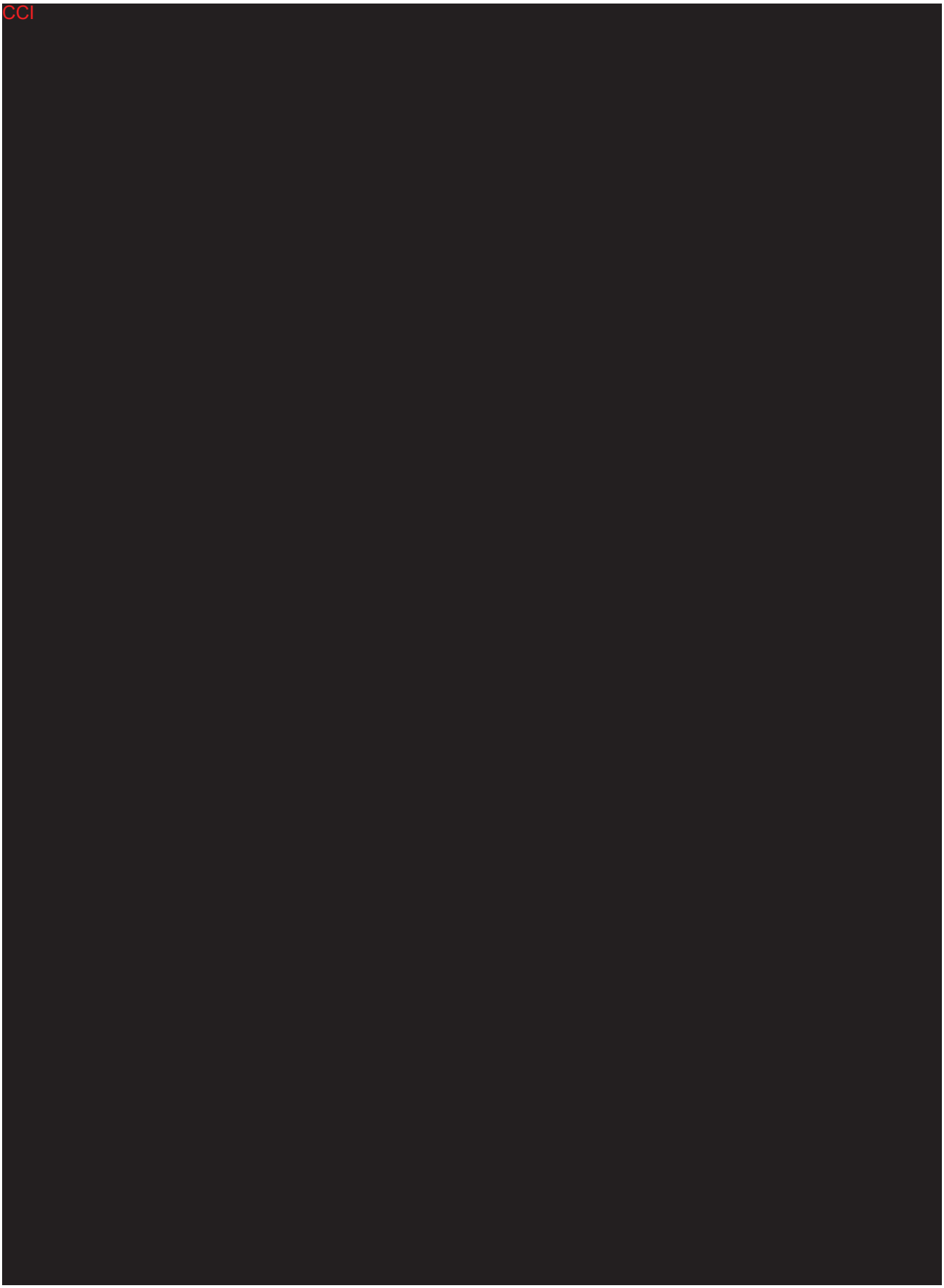
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10.16. Appendix 16: Treatment with Bosentan after PAH-progression

10.16.1. Introduction

Participants with PAH-progression and not treated with an endothelin receptor antagonist (eg, bosentan, ambrisentan) at the time of randomization or during the study, will be offered treatment with bosentan, 32 mg dispersible tablets, provided by the sponsor.

The neurohormone endothelin-1 (ET-1) belongs to a family of 21-amino-acid peptides released from the endothelium and is one of the most potent vasoconstrictors known. Endothelin-1 also promotes fibrosis, cell proliferation, and remodeling, and acts pro-inflammatorily. Endothelin-1 concentrations in tissues and plasma are increased in several cardiovascular disorders and connective tissue diseases, including PAH, scleroderma, acute and chronic heart failure, myocardial ischemia, systemic hypertension, and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In PAH and heart failure, elevated ET-1 concentrations are strongly correlated with disease severity and prognosis (Giaid 1993).

Bosentan is an endothelin receptor antagonist that competes with the binding of ET to both ET_A and ET_B receptors, with slightly higher affinity for the ET_A receptors (K_i = 4.1–43 nM) than for ET_B receptors (K_i = 38–730 nM). By inhibiting the binding of ET to its receptors, bosentan can reduce or attenuate the deleterious consequences of over-produced ET in these pathological states (Bosentan IB). Bosentan decreases both pulmonary and systemic vascular resistance, resulting in increased cardiac output without increasing heart rate.

As of 19 November 2016, bosentan had been approved in 68 countries/territories. Bosentan dispersible tablets have been approved in 36 countries/territories: EEA countries/territories, the US, Switzerland, Mexico (trade name Zuxtana®), Japan, and Russia.

10.16.2. Rationale

Please refer to Section 4.2 for the rationale of providing bosentan following PAH progression.

10.16.3. Background

Nonclinical Studies

Pharmacologic Profile

The absolute bioavailability of bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3–5 hours and the apparent elimination half-life is 5.4 hours as determined after oral administration of a single dose of 125 mg bosentan in healthy participants. Bosentan is highly bound to plasma proteins, mainly albumin. Upon multiple dosing, steady-state is reached within 1 week of treatment (Dingemanse 2004).

Bosentan is eliminated by biliary excretion following metabolism in the liver by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4.

Bosentan is a mild to moderate inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19, and may accelerate the metabolism of drugs which are substrates of these isoenzymes (Bosentan IB).

In addition, glibenclamide (glyburide), calcineurin inhibitors, sirolimus, and fluconazole are contraindicated with the use of bosentan (Dingemanse 2004).

Toxicology

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenicity. Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

Bosentan treatment resulted in dose-related teratogenic effects in rats but not in rabbits. The similarities of the pattern of malformations observed with other ERAs and in ET knock-out mice indicate that this is a class effect. Appropriate precautions should be taken for female participants of childbearing potential.

A moderate increase in the incidence, though not the severity, of slight-to-minimal testicular tubular atrophy was observed in rats during a 2-year carcinogenicity study. The incidence of slight-to-minimal testicular tubular atrophy was within the historical ranges of vehicle-treated controls of the same strain from the same test facility. There were no increases in the incidence of testicular tubular atrophy in marmosets, rats, or dogs in studies of up to 12 months duration. When tested in chronic or reproductive toxicity studies, fertility was normal, as were sperm motility and count, testis and epididymal weights, and histology.

A safety study evaluated the effect on testicular function of bosentan 62.5 mg bid for 4 weeks, followed by 125 mg bid for 5 months in 25 male participants with WHO FC III and IV PAH and normal baseline sperm count. Sperm count remained within the normal range in all 22 participants with data after 6 months, and no changes in sperm morphology, sperm motility, or hormone levels were observed. One of 23 evaluable participants developed oligospermia at 3 months. The sperm count had returned to baseline levels 2 months after discontinuation of bosentan.

A juvenile toxicology study in rats also did not reveal any concerns for the clinical use of bosentan. (Bosentan IB).

Clinical Studies

Human Pharmacokinetics

In study AC-052-116, the PK of bosentan were compared following administration of two distinct formulations (adult, 1×62.5 mg vs pediatric, 2×32 mg) of bosentan in healthy adult male participants. Following dose-normalization, the systemic exposure to all analytes was on average slightly lower in participants treated with the pediatric formulation. This translated in lower C_{max} and AUC values when compared to those obtained after treatment with the adult formulation. However, considering the high inter-subject variability in exposure to bosentan and Ro 48-5033

(without variation in efficacy) observed in study AC-052-365 (FUTURE 1), when bosentan was administered in its pediatric formulation to pediatric PAH participants, the slight decreases in exposures to both analytes after administration of the pediatric formulation were not considered clinically relevant.

In addition, in two previous separate studies, the administration of bosentan at 2 mg/kg bid, in either its pediatric (AC-052-365, FUTURE 1) or adult form (AC-052-356, BREATHE-3) to pediatric PAH participants, resulted in comparable plasma concentrations of bosentan, further indicating that the adult and the pediatric formulations have similar PK profiles.

Bosentan plasma concentrations in children with PAH aged 3 months-<12 years remained on average lower than in adult participants and did not increase when the dosing frequency was increased from 2 mg/kg bid to 2 mg/kg three times a day (tid). The 32 mg bosentan dispersible formulation was administered to neonates with persistent pulmonary hypertension of the newborn via a naso- or orogastric tube at 2 mg/kg bid. Steady-state conditions were attained on Day 5 and the exposure to bosentan was similar to that observed in adults administered bosentan 125 mg bid (Bosentan IB).

Efficacy/Safety Studies

Two pivotal trials in PAH showed a significant improvement in exercise capacity (6MWD) and symptoms in participants with primary PAH and pulmonary hypertension secondary to scleroderma with class III functional status (WHO classification) with bosentan (Channick 2001; Rubin 2002). Both trials (AC-052-351 and AC-052-352) were randomized, double-blind and placebo-controlled, conducted in 32 and 213 participants, respectively, with severe (WHO FC III-IV) PAH. AC 052-351 showed that treatment with bosentan led to a significant increase in cardiac index associated with a significant reduction in pulmonary artery pressure, PVR, and mean right atrial pressure. Consistent with these findings, the EARLY trial (AC-052-364) also demonstrated significant improvement of PVR, significant delay in time to clinical worsening, and a positive trend in 6MWD in participants with mildly symptomatic PAH (WHO FC II) when treated with bosentan (Galiè 2008).

BREATHE-3 (Barst 2003) was an open-label, non-comparative PK, tolerability, safety, and efficacy study in 19 pediatric participants (3-15 years) with PAH (idiopathic and secondary to congenital heart disease). Participants were stratified for body weight and epoprostenol use. Ten participants were treated with stable intravenous epoprostenol throughout the study. Participants received the adult film-coated formulation of bosentan at a dose of 1.5-3.1 mg/kg body weight bid, with the aim of obtaining an exposure to bosentan comparable to adult PAH participants treated with bosentan 125 mg bid.

The exposure to bosentan (expressed as the $AUC_{0\text{-}24h}$) was 43%, 67%, and 75% of the exposure seen in adult participants, respectively, for participants with a body weight of 10-20 kg, 20-40 kg, and >40 kg. These PK data suggested that these participants might have received sub-optimal doses of bosentan.

In the BREATHE-3 study, hemodynamic parameters were also improved after 12 weeks of treatment with bosentan: mPAP and PVR index decreased significantly, whereas the improvement in cardiac index did not reach statistical significance.

Aiming to reach equivalent exposure to bosentan in pediatric PAH participants when compared to adult PAH participants, FUTURE 1, a multicenter, prospective, open-label, non-controlled study was conducted in 36 children with idiopathic or heritable PAH in WHO FC II and III (Beghetti 2009). Participants were treated with the pediatric dispersible formulation of bosentan for 4 weeks at a dose of 2 mg/kg body weight bid followed by 8 weeks at a dose of 4 mg/kg body weight bid The PK profile was assessed in 35 participants at the 4 mg/kg dose only, and 11 participants at both doses. Confirming the results of BREATHE-3, bosentan plasma concentrations in children were lower than those in adults, despite doubling the dose from 2 to 4 mg/kg body weight bid. In addition, time profiles of bosentan following administration of doses of 2 and 4 mg/kg overlapped in the 11-participant subgroup, suggesting that an exposure plateau was reached at a dose of 2 mg/kg bid.

Exploratory efficacy and QoL analyses, ie, WHO fFC, QoL questionnaire and Global Clinical Impression Scale (GCIS; completed by parents and investigators) indicated that most participants in this study remained unchanged from baseline to End of Study.

Study AC-052-373 (FUTURE 3) was an open-label study primarily designed as a PK study evaluating whether an increased dosing frequency from bid to tid with the bosentan dispersible tablet formulation would result in an increased bosentan exposure in pediatric participants with PAH. A total of 64 participants with PAH from 3 months to <12 years of age were randomized to bosentan 2 mg/kg bid (n=33) or 2 mg/kg tid (n=31). The etiology of PAH included iPAH (46%), heritable PAH (3%), associated PAH (38%) and PAH-congenital heart disease (CHD) associated with systemic-to-pulmonary shunts (13%), and participants were WHO FC I (n=16, 25%), II (n=30, 47%) or III (n=18, 28%) at baseline. The median exposure to study treatment was 24.1 (range: 6.0 to 26.4) weeks in the bid group and 24.3 (range: 0.4 to 28.7) weeks in the tid group. The majority of participants remained at least stable (ie, without deterioration) in WHO FC (97% bid, 100% tid) and physician's GCIS (94% bid, 93% tid) during the treatment period. The KM event-free estimate for worsening of PAH (death, lung transplantation, or hospitalization for PAH progression) at six months was 96.9% and 96.7% in the bid and tid groups, respectively.

Study AC-052-374 (FUTURE 3 Extension) was the extended observation of FUTURE 3 participants for 12 months following the core study, allowing additional PAH-specific therapy in the event of PAH worsening. Overall, the results of the cumulative analysis of exploratory efficacy data from these two studies (median duration of exposure 72.2 weeks) suggest that the clinical stabilization observed in the majority of participants in the FUTURE 3 study was maintained (Clinical Study Report AC-065-373 2014). These results are in line with the known efficacy of bosentan in pediatric participants with PAH. The majority of participants had their WHO FC status unchanged from baseline (Month 12: 73.4%, Month 18: 78.1%). Observations made for changes in WHO FC were supported by the physician's GCIS rating, as well as that of parents/legal representatives. The KM event-free estimates for worsening of PAH (death, lung transplantation, or hospitalization for PAH progression) were 84.7% (95% CL: 72.6%, 91.7%) at

Month 12 and 77.4% (95% CL: 64.2%, 86.2%) at Month 18. In the survival analysis of all deaths up to EOS, the overall KM estimates for survival were 85.7% (95% CL: 74.3, 92.3) at Month 12 and 80.9% (95% CL: 68.7, 88.6) at Month 18. In the analysis of 'on-treatment deaths', the overall KM estimates for survival were 87.9% (95% CL: 76.2, 94.0) at Month 12 and 82.3% (95% CL: 69.5, 90.1) at Month 18.

The main safety issues with bosentan treatment are increased incidences of elevated liver enzymes, decreased hemoglobin concentration, and fluid retention.

From preclinical studies, the elevations in liver aminotransferases are thought to be due to bosentan's competitive inhibition of bile salt transport, which is also inhibited by glibenclamide (glyburide). In an integrated analysis of 17 placebo-controlled studies, elevations in ALT and/or AST by more than 3 times the upper limit of normal (ULN) were observed in 11% of bosentan-treated participants compared to 2.5% of placebo-treated participants. Bilirubin increases to >3 times ULN were associated with aminotransferases increases in 0.3% of participants treated with bosentan. Elevations of AST and/or ALT associated with bosentan are dose dependent and may occur early or late in treatment. These elevations are usually asymptomatic and responsive to decrease in bosentan dose or treatment cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with bosentan.

Treatment with bosentan caused a dose related decrease in hemoglobin and hematocrit. The reason for the change in hemoglobin concentration is not fully understood but could be related to hemodilution. There is no evidence for hemorrhage, hemolysis, or bone marrow toxicity.

In severe chronic heart failure participants during the first weeks of treatment, fluid retention (weight gain, leg edema) was observed, resulting in more hospitalizations.

The pediatric experience with bosentan has not given rise to new safety concerns. Reported AEs have been those expected according to the participants' PAH condition, and those AEs already identified to be associated with bosentan in adult participants with PAH treated long-term with bosentan. Notably, there are no indications of an increased risk of liver toxicity, clinically relevant anemia, fluid retention edema or other adverse drug reactions in children compared with adult participants.

In conclusion, the safety and efficacy profile of bosentan in pediatric participants with PAH is commensurate with that which has been well established in multiple clinical trials and long-term post-marketing experience in the adult population.

More detailed information on bosentan is given in the Investigator's Brochure (Bosentan IB).

10.16.4. Eligibility Criteria

Each potential participant must satisfy all of the following criteria for the treatment with bosentan:

Inclusion criteria

A CEC-confirmed event of PAH progression, OR

Need for new PAH-specific therapy AND at least 1 of the following criteria denoting PAH disease progression, judged by the investigator:

- Worsening in WHO functional class (FC), or
- New occurrence or worsening of syncope (in frequency or severity as per medical judgement), or
- New occurrence or worsening of at least two PAH symptoms (i.e., shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue) , or
- New occurrence or worsening of signs of right heart failure not responding to oral diuretics.

Exclusion criteria

A AST and/or ALT values > 3 times the upper limit of normal range.

B Known intolerance or hypersensitivity to bosentan or any of the excipients of the dispersible Tracleer tablet.

C Treatment with forbidden medication within 2 weeks, or at least 5 times the half-life, prior to treatment with bosentan, whichever is the longest:

- Glibenclamide (glyburide)
- Cyclosporin A
- Sirolimus
- Tacrolimus
- Fluconazole
- Rifampicin (rifampin)
- Ritonavir
- Co-administration of CYP2C9 inhibitors (eg, amiodarone, voriconazole) and moderate/strong CYP3A4 inhibitors (eg, amprenavir, erythromycin, ketoconazole, diltiazem, itraconazole)

D Previous treatment with endothelin receptor antagonists (including bosentan) from randomization up to disease progression.

E Pregnancy/breastfeeding and participants not willing/able to comply with contraceptive requirements.

10.16.5. Study Intervention Administered

Designation	Product
AxMP	Bosentan 32 mg dispersible quadrisected tablets Authorization status in the EU : Authorized: bosentan

If participants after PAH-progression are eligible for treatment with bosentan in the context of this study, they may receive the pediatric dispersible oral formulation of bosentan at a dose of 2 mg/kg bid.

Auxiliary Medicinal Product bosentan will be provided as an oral dispersible tablet containing 32 mg bosentan in a blister and a secondary package. The oral dispersible tablet is quadrisected and clover-shaped and breaks into 4 equal 8 mg sections.

The bosentan dosage will be adjusted to the participant's body weight at initiation of the study intervention and at any visit thereafter as needed (Table 7).

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

Bosentan will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure (Bosentan IB) and (TRACLEER® SmPC for a list of excipients.

Bosentan (whole tablet and/or fractions) should be administered orally, dispersed in approximately 5 mL (1 teaspoon) of water per 2 tablets (not mixed with food) before being administered irrespective of meals. It will be taken in the morning and approximately 12 hours later in the evening.

Participants/parent/LAR will be instructed that if one or more bosentan doses are missed, these should be regarded as missing and no attempt should be made to make up for these missing doses. The administration of bosentan should resume as soon as possible.

Table 7: Bosentan Dosage scheme according to the participant's body weight

Body weight, kg (to be checked at each visit)	mg (bosentan)	Number T and Q per dose administration
9	16	2Q
10	16	2Q
11	24	3Q
12-13	24	3Q
14	24	3Q
15	32	**1T**
16-17	32	**1T**

Body weight, kg (to be checked at each visit)	mg (bosentan)	Number T and Q per dose administration
18	32	**1T**
19	40	**1T**+1Q
20-21	40	**1T**+1Q
22	40	**1T** +1Q
23	48	**1T**+2Q
24-25	48	**1T+**2Q
26	48	**1T**+2Q
27	56	**1T**+3Q
28-29	56	**1T**+3Q
30	56	**1T**+3Q
31	64	**2T**
32-33	64	**2T**
34	64	**2T**
35	72	**2T**+1Q
36-37	72	**2T**+1Q
38	72	**2T**+1Q
39	80	**2T**+2Q
40-41	80	**2T**+2Q
42	80	**2T**+2Q
43	88	**2T**+3Q
44-45	88	**2T**+3Q
46	88	**2T**+3Q
47	96	**3T**
48-49	96	**3T**
50	96	**3T**
51	104	**3T**+1Q
52-53	104	**3T**+1Q
54	104	**3T**+1Q
55	112	**3T**+2Q
56-57	112	**3T**+2Q
58	112	**3T**+2Q
≥59	120	**3T**+3Q

T = Tablets Q = Quarters

10.16.6. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Refer to the site Investigational Product binder/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Accountability

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

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

Bosentan should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Bosentan will be supplied only to participants participating in the study. The participants will receive sufficient supply to cover the period up to the next scheduled visit. Returned medication must not be dispensed again, even to the same participant. Bosentan may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense bosentan from, nor store it at, any site other than the study sites agreed upon with the sponsor.

10.16.7. Bosentan Allocation

Bosentan allocation

Bosentan will be provided in an open-label fashion. The IWRS will assign unique bosentan kit numbers for each applicable visit.

10.16.8. Bosentan Compliance

Compliance to bosentan treatment is based on study intervention accountability (refer to Section 10.16.6). Site personnel will enter the number of tablets returned in IWRS. Bosentan compliance will be calculated by the sponsor using the below formula:

$$\text{Compliance} = \frac{\text{Number of tablets dispensed} - \text{Number of tablets returned}}{\text{Total number of tablets that should have been taken during the period}^{*}} \times 100$$

* The period is defined as the number of days of treatment from the date of dispensation of bosentan until the next accountability visit. The number of tablets that should have been taken should be calculated on a participant basis, based on the investigator's prescription.

10.16.9. Concomitant Therapy

Prohibited Concomitant Therapy

The following treatments are prohibited while treatment with bosentan is ongoing:

- Glibenclamide (glyburide)
- Cyclosporin A
- Sirolimus
- Tacrolimus
- Fluconazole
- Rifampicin (rifampin)
- Ritonavir
- Co-administration of CYP2C9 inhibitors (eg, amiodarone, voriconazole) and moderate/strong CYP3A4 inhibitors (eg, amprenavir, erythromycin, ketoconazole, diltiazem, itraconazole)
- Endothelin receptor antagonists other than bosentan.

10.16.10. Discontinuation of Treatment with Bosentan

Treatment with bosentan must be discontinued if:

- The participant withdraws consent or assent to receive bosentan.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue bosentan.
- The participant becomes pregnant (refer to Section 10.6, Contraceptive and Barrier Guidance).
- Treatment with prohibited medications is initiated.

Bosentan bottles/kits assigned to the participant who discontinued bosentan may not be assigned to another participant.

10.16.11. Temporary Discontinuation

Interruption of treatment with bosentan might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (eg, ECG or laboratory abnormalities), or for administrative reasons. The reason for interruption must be documented in the CRF.

10.16.12. Safety Assessments

Study assessments during the study are described in Sections 1.3.2, 1.3.3, 1.3.4, and 8. The below describes additional mandatory safety assessments while a participant is receiving bosentan.

Liver function tests must be performed at 4-week intervals until one month after bosentan treatment discontinuation.

If a clinically-relevant increase in liver function test occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment.

ALT and/or AST	Treatment and monitoring recommendations
>3 and ≤5×ULN	Confirm by another liver test. If confirmed, interrupt treatment with bosentan, monitor aminotransferase, bilirubin and alkaline phosphatase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
>5×ULN	Treatment with bosentan must be stopped, and re-introduction of study treatment is not to be considered. Monitor aminotransferase, total and direct bilirubin and alkaline phosphatase levels at least every 2 weeks up to their return to pre-treatment values.

ULN = Upper Limit of Normal

In case of associated clinical symptoms of liver injury, eg, nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), and/or increases in total bilirubin ≥2 × ULN, bosentan must be stopped and re-introduction is not to be considered.

Re-introduction of bosentan after treatment interruption should only be considered if the potential benefits of treatment with bosentan outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended.

Liver aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks and thereafter according to the recommendations above, ie, at 4-week intervals.

Other diagnoses should be considered and ruled out by performing the appropriate tests (eg, viral hepatitis, etc).

All liver function test abnormalities leading to interruption of bosentan treatment must be recorded as AEs.

All events of aminotransferase ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

Hematology tests must be assessed monthly during the first 4 months of treatment with bosentan and quarterly thereafter.

Pregnancy tests and contraceptive requirements

Prior to initiation of treatment with bosentan, a negative serum pregnancy test is required. Serum pregnancy tests must be performed in female participants of childbearing potential every 4 weeks (± 7 days) until 30 days after bosentan discontinuation. Serum pregnancy tests will replace the 4-weekly urine pregnancy tests in participants receiving study treatment bosentan.

Sexually active female participants of childbearing potential must use an effective method of contraception as described in Section 10.6 until 30 days after bosentan discontinuation.

If a female becomes pregnant while on bosentan, permanent discontinuation of bosentan treatment must be considered. The investigator must counsel the participant and, where allowed under local law, her parent(s)/LAR(s) to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Reporting and follow-up of pregnancy is described in Section 8.6.4.

Adverse Events and Serious Adverse Events

Reporting of AEs is described in Sections 8.6 and 10.5.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours upon knowledge of the event. The investigator must complete the SAE Form in English and must assess the event's causal relationship to the study intervention as well as bosentan. Any relevant information from source documents regarding the SAE (eg, hospital notes, discharge summaries, etc) must be summarized on the SAE Form.

10.16.13. Intervention After the End of the Study

If a participant receives bosentan as described in this appendix, and continued treatment is deemed appropriate by the investigator, bosentan will be provided to these participants during the selexipag OLEP (Section 4.1) and after the selexipag OLEP (if feasible as per local regulations).

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD MD

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

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

P

Signature

User	Date	Reason
PPD	01-Mar-2023 07:24:42 (GMT)	Document Approval
	01-Mar-2023 11:19:12 (GMT)	Document Approval
	01-Mar-2023 13:01:10 (GMT)	Document Approval

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

Clinical Protocol

Appendix to SALTO Study Protocol
GUIDANCE ON STUDY CONDUCT DURING A NATURAL DISASTER/MAJOR DISRUPTION/PANDEMIC

Protocol Title
A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group, Event-Driven, Group-Sequential Study with Open-Label Extension Period to Assess the Efficacy and Safety of Selexipag as Add-On Treatment to Standard of Care in Children Aged ≥2 to <18 years with Pulmonary Arterial Hypertension

SALTO

Protocol AC-065A310; Phase 3

JNJ-67896049 / ACT-293987 (Selexipag)

*Actelion Pharmaceuticals Ltd ("Actelion") is a global organization that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the sponsor for Actelion studies may vary, such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; 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: 2019-002817-21

Status:	Approved
Date:	08 April 2022
Prepared by:	Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson
EDMS number:	EDMS-RIM-263730, 4.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF THE PROTOCOL AC-065A310 (SALTO)

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

GUIDANCE ON STUDY CONDUCT DURING A NATURAL DISASTER/MAJOR DISRUPTION/PANDEMIC

It is recognized that a natural disaster/major disruption/pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be at risk, study attendance may be interrupted, and study follow-up may be conducted remotely. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If scheduled visits cannot be conducted in person at the study site as a result of a natural disaster/major disruption/pandemic, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations.

Natural disaster/Major disruption: 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. Discontinuations of the study interventions and withdrawal from the study should be documented by providing a reason in the case report form (eCRF). Modifications made to the study conduct as a result of the natural disaster or major disruption should be summarized in the clinical study report.

Pandemic: Discontinuations of the study interventions and withdrawal from study should be documented with the prefix "COVID-19-related" in the eCRF. Modifications made to the study conduct as a result of the pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Screening of participants

- Screening of participants is only allowed if, in the investigator's judgment, study visits can occur on-site and following agreement with the sponsor.

- Participants in screening for whom compliance with the per-protocol on-site visit-schedule is expected to be impacted due to local restrictions, must be screen-failed. Re-screening as per protocol section 5.4 (Screen Failures) can be considered if eligibility criteria are met, restrictions are lifted, and on-site visits can resume.

Scheduled Visits (randomized participants)

- When local restrictions do not allow on-site visits, investigators will schedule remote visits within the per protocol requested visit window in order to collect the following data (to the extent possible at a virtual/phone visit) for entering into the eCRF:

  Pulmonary arterial hypertension signs and symptoms (to check for disease progression)

  WHO and PANAMA Functional Class (to check for disease progression)

  Adverse events

  Concomitant therapies

  Childbearing potential (if applicable)

  Counseling for contraception (if applicable)

  Monthly pregnancy tests (if applicable)

  Quality of Life questionnaire (if applicable)

  Study intervention compliance

  Palatability and acceptability of study intervention (if applicable).

The investigator can give study intervention titration instructions as per protocol section 6.1 (Study Interventions Administered) based on the discussion with the participant/parents/legally authorized representative(s) (LARs) during virtual visits, in particular, if a participant is in the study intervention up-titration period.

In addition, the investigator will remind participants/parents/LAR(s) that the accelerometry device should be worn (if applicable for a visit) per protocol.

The investigator will record in the source document that the above-mentioned data have been obtained remotely as well as the instructions provided to the participant/parents/LAR(s).

- When local restrictions do not allow on-site visits, the following assessments can be considered to be performed locally (eg, by "visiting nurse" [contract research organization/Home Health Care (HHC) vendor]) as local regulations permit:
  - Blood sampling and analysis (hematology, chemistry, TSH and NT-proBNP) by a non-site local laboratory (sites may also consider local blood draws by site personnel for analysis at the central or the site's local laboratory).
  - Vital signs (blood pressure/heart rate).
  - Weight and height.
  - Physical examination.

- Documentation of assessments performed via HHC will be provided to the investigator. These reports will serve as source documents for the AC-065A310/SALTO study. The investigator will document that the content was reviewed and adverse events will be reported as appropriate.
- If blood samples are analyzed locally, a copy of the non-site local laboratory certification and the respective reference ranges must be obtained and stored in the Investigator Site File.

Urine Pregnancy Test

- Urine pregnancy tests for females of childbearing potential may be shipped from the site to the participants' home, in case on-site visits are not possible.

Investigational Product (IP)

- In relation to Protocol Section 6.1 (Study Interventions Administered), for participants unable to visit the site, direct-to-patient (DTP) shipment of study intervention (double-blind study treatment and/or bosentan) may be implemented, where allowed per local regulations, and if requested by the investigator.

Informed Consent

- In relation to Protocol Section 10.4, section INFORMED CONSENT PROCESS AND ASSENT FORM, consenting on COVID-19-, major disruptions-, or natural disaster-related changes will be performed and documented as applicable for the measures taken and according to local guidance for informed consent as applicable.

Site Monitoring

- If on-site monitoring is not possible due to local restrictions, monitoring will be done remotely to the extent possible and as outlined in the monitoring guidelines. On-site monitoring will be delayed until after local restrictions are lifted.
- In order to maintain appropriate source data verification and resolution of potential pending issues, on-site monitoring visit frequency and/or duration may be increased after local restrictions are lifted.

Audits

- During the natural disaster/major disruption/pandemic at the impacted sites, clinical site Good Clinical Practice audits with direct impact/engagement with the clinical investigator team will not be conducted to comply with national, local and/or organizational restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement, if possible.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

- Study participants can undergo a COVID-19 vaccination procedure in compliance with applicable local practice/governmental regulations.

- No pharmacokinetic interaction between the study intervention and currently available COVID-19 vaccines are expected. In addition, based on the mechanism of action of the study intervention and COVID-19 vaccines, no relevant interaction is expected.
- Any COVID-19 vaccine administered to a study participant is considered a concomitant medication and should be reported on the electronic case report form (eCRF).
- For serious adverse events (SAEs) reported after COVID-19 vaccination, the investigator should provide narrative details on the SAE form to allow adequate assessment of causality relationship between the reported SAE and vaccination. This is particularly relevant in cases where the reported SAE is an expected event with the study intervention and the COVID-19 vaccine. If the event is serious and considered to be related to both the COVID-19 vaccine and the study intervention, it is a serious adverse reaction and expectedness must be assessed. Suspected unexpected serious adverse reaction (SUSAR) reporting will be performed if the serious adverse reaction is unexpected as per applicable reference safety document.
- Study participants do not require unblinding of the study intervention to receive a COVID-19 vaccine.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals for whom I am responsible who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD, MD

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

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

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

Signature

User	Date	Reason
PPD	08-Apr-2022 14:29:59 (GMT)	Document Approval
	08-Apr-2022 16:40:04 (GMT)	Document Approval
	11-Apr-2022 07:25:39 (GMT)	Document Approval