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

Statistical Analysis Plan for Clinical Study Report

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
Selexipag As an add on therapy for chiLdren with pulmonary arTerial hypertensiOn

Protocol AC-065A310; Phase 3

JNJ-67896049 / ACT-293987 **(**selexipag**)**

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VERSION HISTORY

This statistical analysis plan for Study AC-065A310 is based on the protocol dated 01Mar2023.

SAP Version	Approval Date	Change	Rationale
1.0	09 October 2024	Not Applicable	Initial release

LIST OF ABBREVIATIONS

6MWD	6-minute walk distance
AE	adverse event
AER	annualized event rate
AESI	adverse event of special interest
ALT/SGPT	alanine aminotransferase
aPAH-CHD	pulmonary arterial hypertension associated with congenital heart disease
AST/SGOT	aspartate aminotransferase
ATC	anatomical therapeutic chemical
bid	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CEC	Clinical Event Committee
CHD	congenital heart disease
CHMP	Committee for Medicinal Products for Human Use (European Union)
CSR	clinical study report
CTMS	clinical trial management system
DB	double-blind
DBED	double-blind end date
DBL	Database lock
DBSD	double-blind start date
DPS	Data Programming Specifications
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDBT	End-of-Double-Blind Treatment
e-DISH	evaluation of drug-induced serious hepatotoxicity
EOS	End of Study
EOT	End of Treatment visit
ERA	endothelin receptor antagonist
FAS	Full Analysis Set
FC	functional class
FDA	Food and Drug Administration
GRIPHON	Prostacyclin (PGI_2) receptor agonist in pulmonary arterial hypertension
GSD	group sequential design
HIV	human immunodeficiency virus
hPAH	heritable pulmonary arterial hypertension
HR	hazard ratio
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
iMTD	individual maximum tolerated dose
iPAH	idiopathic pulmonary arterial hypertension
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LAR	Legally authorized representative
LFT	liver function test
LLT	lower level term
mPAP	mean pulmonary arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NT-proBNP	N-terminal pro-brain natriuretic peptide
OL	Open-label
OLEP	Open-label Extension Period
OPAE	observation period adverse event
OPSAE	observation period serious adverse events

OR	odds ratio
PAH	pulmonary arterial hypertension
PAWP	pulmonary arterial wedge pressure
PD	protocol deviation
PDE-5	phosphodiesterase type-5
PedsQL™	Pediatric Quality of Life Inventory™
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PPS	Per-Protocol Analysis set
PT	preferred term
PTAE	post-treatment adverse event
PTOP	post-treatment observation period
PTSAE	post-treatment serious adverse events
PVR	pulmonary vascular resistance
PY	patient years
QoL	quality of life
RHC	right heart catheterization
RMST	restricted mean survival time
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SCR	Screened Analysis Set
SD	standard deviation
SDTM	Study Data Tabulation Model
sGCs	soluble guanylate cyclase stimulator
SI	standard international
SMQs	standardized MedDRA queries
SoC	Standard of Care
SOC	system organ class
SSG	statistical support group
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
uSST	unblinded selexipag sponsor team
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the statistical analyses of efficacy (primary, secondary, and exploratory endpoints) and safety endpoints for the end of the double-blind (DB) period of study AC-065A310 / SALTO. It is based on Version 7 – Global Amendment 5 of the AC-065A310 protocol (EDMS-RIM-265811, 5.0).

Different requirements from Health Authorities have necessitated the creation of separate SAPs for different analysis timepoints of the study (Section 1.2.1). An overview for analysis timepoints 1, 2 and 3 is provided in the table below. Endpoints included in the respective SAPs for these analysis timepoints are described in Section 6.10 Appendix 10. Analysis 3 is the focus of this SAP.

SAP	**Database lock date/ Data cut-off date**	**Features and Purpose**	**Execution**
Analysis 1 EDMS-RIM-1093728, 1.0 08 September 2023	12 September 2023/ 14 August 2023	• A descriptive analysis when 80 participants had been followed up for at least 24 weeks. • To meet a legal Health Authority requirement in one region.	• Conducted by an independent unblinded selexipag sponsor team (uSST) before completion of the DB treatment period. • Details of the uSST membership and conduct were provided in a separate firewall charter, which was finalized and approved prior to the database lock (DBL) for Analysis 1. • The uSST had no further involvement in the conduct of the study or preparation for Analysis 2. • The sponsor study team remained blinded until Analysis 2 after which the results of Analysis 1 were shared with the study team. Site personnel, and participants remain blinded until the end of the DB treatment period, Analysis 3. • See Section 1.2.4.
Analysis 2 EDMS-RIM-218198, 5.0 02 April 2024	9 April 2024/ 19 February 2024	• When all randomized participants had been followed up for at least 24 weeks or prematurely discontinued the study in the DB treatment period. • An inferential analysis, based on NT-proBNP change from baseline to Week 24. • For an interaction with a legal Health Authority in another region. • Also, specification for Analysis 3 included incremental listings only	• Conducted by the sponsor study team, who were unblinded after the DBL for Analysis 2. • Site personnel and participants remain blinded until the announcement of the end of the DB treatment period. • See Section 1.2.4.

		(data collected from the time of the cut-off for Analysis 2 to Analysis 3).	
Analysis 3 EDMS-RIM-1437023, 1.0 09 October 2024	29 October 2024/ Not applicable as all data up to the end of the DB period is included. Participants return for their end of DB visit in a staggered manner. Open-label (OL) data are not included.	• At the end of the DB period. • To facilitate further interactions with health authorities, this SAP specifies comprehensive analyses of all data collected during the DB treatment period and replaces the Analysis 3 specifications (only incremental data listings) in the Analysis 2 SAP. • This SAP has been prepared after the sponsor study team had been unblinded upon DBL for Analysis 2 (as per protocol Section 9.2). • Most of the analyses in this SAP are the same as in the Analysis 2 SAP (finalized prior to unblinding) and will be performed again in Analysis 3 with updated data through the end of the DB period. • See Section 6.10 Appendix 10 for further details.	• Will be conducted by the sponsor study team, who were unblinded after the DBL for Analysis 2. • Site personnel and participants will be unblinded.

Titles, mock-ups, and programming instructions for all statistical outputs (tables, listings, and figures) are provided in a separate data presentation specifications (DPS) document.

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM). All descriptive and inferential statistical analyses will be performed using SAS® (Version 9.4) or R software (Version 4.2.1), unless otherwise specified.

1.1. Objectives

Section 3 of the protocol outlines the objectives and endpoints of the study.

The primary objective is:

- to evaluate whether the addition of selexipag to Standard of Care (SoC) treatment delays disease progression in children with Pulmonary Arterial Hypertension (PAH) in comparison to placebo.

Secondary objectives are:

- to evaluate whether the addition of selexipag to SoC treatment decreases NT-proBNP in children with PAH in comparison to placebo,
- to assess the safety and tolerability of selexipag in children with PAH,
- to evaluate whether selexipag can delay hospitalization and death due to PAH worsening in children with PAH,
- to assess the trough plasma concentrations of selexipag and its active metabolite at steady state in children with PAH.
- The statistical hypotheses for the primary objective and the secondary objectives are detailed in Sections 2.1 and 2.2 and the aligned estimands are defined in Sections 4.2.1.2, 4.3.1.1.2 and 4.3.2.2.

1.2. Study Design

Section 4 of the protocol outlines the detailed study design considerations.

An overview of the design of the study is provided in Figure 1 below.

This is a randomized, multicenter, DB, placebo-controlled, parallel-group study with an open-label extension period (OLEP) to assess the efficacy and safety of selexipag as add-on to SoC in children aged ≥2 to <18 years with PAH.

Participants are enrolled 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.

A participant's cohort was determined by age at the time of Interactive Web Response System (IWRS) randomization.

Enrollment started with 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) at the time of SALTO study initiation. Enrollment into age cohort 3 (≥2 to <6 years of age) was initiated after the starting dose and uptitration regimen was confirmed in the corresponding age cohort of AC-065A203 (PK Final Analysis Report AC-065A203 2022).

1.2.1. Analysis Timepoints

Within the study, a set of 4 analyses are planned:

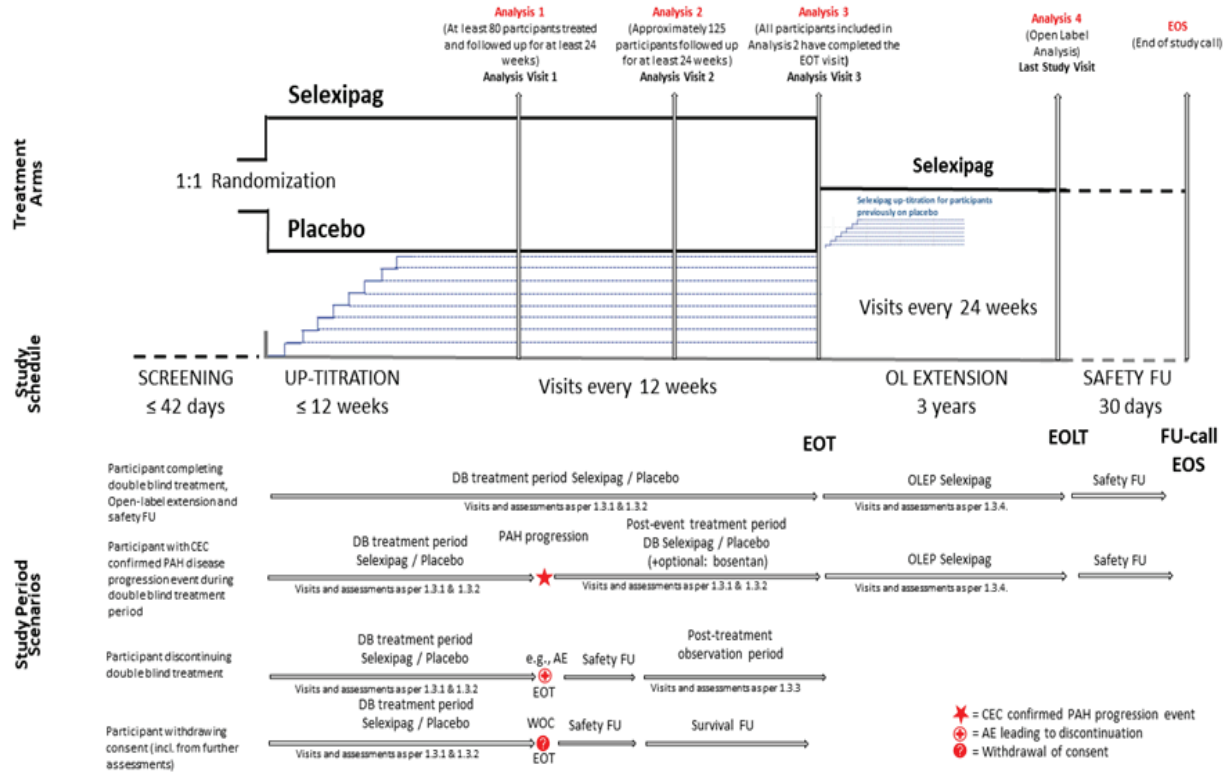
- Analysis 1: CCI [redacted] with data cut-off date when at least 80 participants had been treated and followed up for at least 24 weeks in the DB treatment period. Data from all participants were included in this analysis, including data from participants who prematurely discontinued the study in the DB treatment period prior to 24 weeks. Analysis 1 was performed and reported by an independent

unblinded [redacted] team to [redacted] before completion of the DB treatment period. The study team remained blinded to the results of this analysis (see Section 1.2.3 and Section 1.2.4). This analysis is not in scope of this SAP and is detailed in a separate SAP (EDMS-RIM-1093728, 1.0).

- Analysis 2: [redacted] with data cut-off date that occurred when all randomized participants had been followed up for at least 24 weeks or prematurely discontinued the study in the DB treatment period. This analysis was required for an interaction with a legal Health Authority in another region. The full sponsor study team was unblinded after DBL for Analysis 2. Site personnel and participants remained blinded until the announcement of the end of the DB treatment period (see the following bullet and Section 1.2.3 and Section 1.2.4). All study participants (except those who had prematurely discontinued DB study intervention) remained on DB intervention until the announcement of the end of the DB treatment period. Analyses were performed according to the respective SAP (EDMS-RIM-218198, 5.0).
- Analysis 3: Analysis at the end of the DB treatment (EDBT) period, after all participants included in Analysis 2 complete their end of treatment (EOT) visit. Site personnel and participants will be unblinded. Analysis 3 is the focus of this SAP. There is no prespecified single cut-off date for Analysis 3:
- All data from the DB period will be included.
- For participants entering the OLEP, a technical cut-off will be applied to SDTM data sets, excluding OL data with a date after OL Day 1 [these participants will enter the OLEP in a staggered manner and are expected to have their last DB treatment administration (morning dose) on the same day as their first OL selexipag administration (evening dose)].
- For participants who do not enter the OLEP, no technical cut-off is required as all data are part of the DB period, including the post-treatment observation period (PTOP), Safety Follow-up period/End of Study (EOS) call and Survival Follow-up data, performed prior to the DBL.
- Analysis 4: As per protocol Section 2.3, following an assessment of the benefit-risk for treating children with PAH with selexipag, the sponsor announced the EDBT period and an OLEP was initiated on 10 July 2024. The OLEP is planned, per protocol, to continue for up to 3 years from the first participant entering the OLEP. Treatment with OL selexipag is offered to all participants eligible for the OLEP. Participants will enter the OLEP in a staggered manner when they complete their DB treatment period. Analysis of the OLEP will occur after all participants have completed up to 3-year of OLEP or have prematurely discontinued the study. This analysis is not in scope of this SAP.

A schematic overview of the timing of the 4 analyses is provided in Figure 1.

Figure 1: Schematic Overview of the Analysis Timepoints



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.

1.2.2. Participant Follow-Up, Study Periods and Schedule of Assessments

See Section 4.1 of the protocol for details of consecutive study periods and milestones.

See Section 1.3 of the protocol for full details of the visit and assessment schedule.

A schematic overview of the study design is provided in Figure 1.

1.2.3. Randomization and Blinding

1.2.3.1. Randomization and Stratification

See Section 6.3 of the protocol.

Central randomization was implemented in this study. Participants were randomly assigned in a 1:1 ratio to 1 of 2 study interventions (placebo or selexipag), based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor. The randomization list included enough randomization slots to avoid any possible extension request during the study. Jumbled randomization numbers were used to avoid any possible unblinding that could come from the knowledge of the assigned treatment code.

The randomization was balanced by using randomly permuted blocks and was stratified by:

- World Health Organization Functional Class (WHO FC) (II vs III) at randomization, and
- PAH-specific treatment (monotherapy vs combination therapy) at randomization.

The IWRS assigned a unique intervention code, which dictated the intervention assignment and matching study intervention kit for the participant. The requestor used his or her own user identification and personal identification number when contacting the IWRS and provided the relevant participant details to uniquely identify the participant.

Block size was not known by investigator, site, or study team members with exception of the study statistician that reviewed and approved the randomization list requirement.

1.2.3.2. Blinding

See Section 6.3 of the protocol.

The study team remained blinded until the DBL for Analysis 2. An independent submission team was unblinded to the data to perform Analysis 1 to prepare for interactions with selected Health Authorities. Details were provided in a separate firewall charter, which was finalized and approved prior to the DBL for Analysis 1.

Following the sponsor announcement of the EDBT period (see Section 1.2.1), sites were informed to request that participants return for their EDBT period assessment and the OLEP was initiated. Uptitration of OL intervention is applied only for participants previously on placebo in the DB period, hence for participants entering the OLEP sites were unblinded by the IWRS set up for OL visits.

Further details are provided in Section 1.2.4.

1.2.4. Minimization of Bias

Analysis 1 (Section 1.2.1) was performed by an independent unblinded submission team to meet a legal Health Authority requirement in one region before completion of the DB treatment period. The study team remained blinded to this analysis. Details of the individual teams and the plan for protecting the study team from the unblinding information and results of Analysis 1 were documented in a separate firewall charter, which was finalized prior to DBL for Analysis 1.

The study team was unblinded only after the DBL for Analysis 2. Site personnel and participants will remain blinded until the announcement of the EDBT period.

Unblinded analyses for the Independent Data Monitoring Committee (IDMC) closed sessions are documented in a separate SAP. This is written and maintained, and analyses performed by an independent, unblinded statistical support group (SSG) (see Section 4.7.1.1 and IDMC Charter Section 8 for details).

2. STATISTICAL HYPOTHESES

2.1. Primary Hypothesis

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

The statistical hypotheses for the primary endpoint of time to first occurrence of CEC-confirmed disease progression event up to 7 days after study intervention discontinuation are formulated as follows:

$$H_0: S_{dp,selexipag}(t) \leq S_{dp,placebo}(t),\ t \geq 0$$
$$\text{vs.}$$
$$H_a: S_{dp,selexipag}(t) > S_{dp,placebo}(t),\ t \geq 0$$

where,

$S_{dp,selexipag}(t)$ is the survival function of time to disease progression in the selexipag group and

$S_{dp,placebo}(t)$ is the survival function of time to disease progression in the placebo group.

The null hypothesis is that selexipag as compared to placebo does not further delay the time to first CEC-confirmed disease progression event. The alternative hypothesis is that selexipag as compared to the placebo, further delays the time to first CEC-confirmed disease progression event.

2.2. Secondary Hypotheses

The hypotheses for the secondary efficacy endpoints are described as follows:

Secondary Endpoint	Hypothesis
Change in $\log_2$(NT-proBNP) from baseline to Week 24 (expressed as $\log_2$(Week24/baseline))	The null hypothesis (H_{01}) is that there is no difference between selexipag and placebo for the change from baseline to Week 24 in $\log_2$(NT-proBNP) $H_{01}: \Delta = \mu_{selexipag,24} - \mu_{placebo,24} = 0.$ The alternative hypothesis (H_{11}) is that there is a difference between intervention groups $H_{11}: \Delta = \mu_{selexipag,24} - \mu_{placebo,24} \neq 0.$
Time to first occurrence of CEC-confirmed death or hospitalization due to PAH up to 7 days after the last dose of DB study intervention	The null hypothesis (H_{02}) is that there is no difference between the selexipag and placebo survival distributions ie, S(t) or that the difference favors placebo $H_{02}: S_{selexipag}(t) \leqslant S_{placebo}(t),\ t \geqslant 0.$ The alternative hypothesis (H_{12}) is that there is a difference between intervention groups in favor of selexipag $H_{12}: S_{selexipag}(t) > S_{placebo}(t),\ t \geq 0.$

2.3. Multiplicity Adjustment

Hypothesis testing was performed for the secondary endpoint NT-proBNP change from baseline to Week 24 at Analysis 2 and reproduced for Analysis 3. Hypothesis testing outcomes for other endpoints are considered exploratory. Hence, no adjustment for multiplicity is made.

3. ANALYSIS SETS

Table 1 defines all analysis sets for analyses of the DB treatment period. All efficacy endpoints will be evaluated on the Full Analysis Set (FAS). The Per-Protocol Analysis Set (PPS) will be used only for the secondary endpoint NT-proBNP change from baseline to Week 24. Safety endpoints will be primarily evaluated on the Safety Analysis Set (SAS).

Table 1: Overview of Analysis Sets

Analysis Set	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. All main statistical analyses of all efficacy endpoints are based on the FAS, in order to adhere to the intention-to-treat principle as much as possible. Participants are evaluated according to the study intervention they have been randomized to (which may be different from the study intervention they have received).
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 intervention effects. The PPS comprises participants included in the FAS who: • received at least one dose of DB study intervention • did not interrupt study intervention (according to study intervention information in the eCRF) for a total of at least 50% of the time between first DB study intervention intake and the earlier of (last DB study intervention intake and Week 24) • have not been off intervention for greater than 2 consecutive weeks at any point between first dose of DB study intervention and the earlier of (last DB study intervention intake and Week 24) • did not experience a major PD marked as leading to exclusion from per-protocol set in the AC-065A310_Major PD Criteria Form. Participants are evaluated according to the study intervention they have been randomized to.
Safety Analysis Set (SAS)	All participants who received at least one dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual assessment visits (including scheduled and unscheduled visit results) to analysis visits. Listed below are the analysis visit windows and the target days for each actual assessment/scheduled visit up to end of the DB period or start of OL Day 1 [where participants who transition to the OLEP are expected to have their last DB treatment administration (morning dose) on the same day as their first OL selexipag administration (evening dose) of OL Day 1]. The reference day is Study Day 1, as defined in Section 4.1.8. If a participant has 2 or more actual assessment visits in an analysis visit window, the visit closest to the target day and within the specific treat evaluation period will be used as the protocol visit for that analysis visit window. The other additional visit(s) will not be used in the summaries or analyses by visit, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within an analysis visit window, the later visit is used. If more than 1 value falls on the same day then the worst value will be used for categorical variables (higher or lower value, depending on the parameter, a separate document to be utilized for programming purposes will include a table to map which parameters will take on higher/lower values, respectively), while the average value will be calculated for continuous variables.

All assignments will be made in chronological order. Once a visit date is assigned to an analysis visit window, it will no longer be used for a later time point. Listed below (Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8) are the analysis visit windows and the target study days for each visit defined in the protocol.

All assessments considered for analysis visit windows as described below must occur in the DB period/OL Day 1 (for those participants who enter OLEP) to which they are being assigned.

All assessments corresponding to both scheduled and unscheduled visits will be included in participant listings.

Table 2: Scheduled Visits and Analysis Visit Windows for WHO FC, Panama FC, Vital signs, Thyrotropin/ Thyroid-stimulating hormone (TSH), Tanner Stage[$], and Childbearing Potential Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day[*])	Analysis Visit Window (Day[*])
Screening	Visit 1		Screening	Up to -1	< 1
DB	Baseline/Visit 2	Day 1	Baseline	1	[−42 to 1][#]
	Visit 3	Week 4	Week 4	28	[2 to 42]
	Visit 4	Week 8	Week 8	56	[43 to 70]
	Visit 5	Week 12	Week 12	84	[71 to 98]
	Visit 6	Week 16	Week 16	112	[99 to 140]
	Visit 7	Week 24	Week 24	168	[141 to 210]
	Visit 8	Week 36	Week 36	252	[211 to 294]
	Visit 9	Week 48	Week 48	336	[295 to 378]
	Visit 10	Week 60	Week 60	420	[379 to 462]
	...				
	Visit x	Week n	Week n	n*7	[n*7 – 41 to n*7 + 42]

[$]Scheduled post-baseline visits for Tanner stage are from Visit 6 up until protocol Version 5 – Global Amendment 4 and from Visit 7 from protocol Version 6 – Global Amendment 5. [#]Lower limit for baseline assessment for Tanner Stage could be before Day -42 and therefore lower limit is not applied.
[*]Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in the PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).
DB = Double-blind.

Table 3: Scheduled Visits and Analysis Visit Windows for Weight and Height Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day[*])	Analysis Visit Window (Day[*])
Screening	Visit 1		Screening	Up to -1	< 1
DB	Baseline/Visit 2	Day 1	Baseline	1	[−42 to 1]
	Visit 5	Week 12	Week 12	84	[2 to 98]
	Visit 6	Week 16	Week 16	112	[99 to 140]
	Visit 7	Week 24	Week 24	168	[141 to 210]
	Visit 8	Week 36	Week 36	252	[211 to 294]
	Visit 9	Week 48	Week 48	336	[295 to 378]
	Visit 10	Week 60	Week 60	420	[379 to 462]
	...				
	Visit x	Week n	Week n	n*7	[n*7 – 41 to n*7 + 42]

[*]Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in the PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).
DB = Double-blind.

Table 4: Scheduled Visits and Analysis Visit Windows for NT-proBNP Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day*)
Screening	Visit 1		Screening	Up to -1	< 1
DB	Baseline/Visit 2	Day 1	Baseline	1	[−42 to 1]
			Up-titration#	84	[2 to 84]
	Visit 6	Week 16	Week 16	112	[85 to 140]
	Visit 7	Week 24	Week 24	168	[141 to 252]
	Visit 9	Week 48	Week 48	336	[253 to 420]

*Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).
#Assessments completed in this time interval will be presented in listings but not included in analyses.
DB = Double-blind.

Table 5: Scheduled Visits and Analysis Visit Windows for 6-minute walk distance (6MWD) Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day*)
Screening	Visit 1		Screening	Up to -1	< 1
DB	Baseline/Visit 2	Day 1	Baseline	1	[−42 to 1]
	Visit 6	Week 16	Week 16	112	[2 to 140]
	Visit 7	Week 24	Week 24	168	[141 to 252]
	Visit 9	Week 48	Week 48	336	[253 to 420]

*Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in the PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).
DB = Double-blind.

Table 6: Scheduled Visits and Analysis Visit Windows for Quality of Life and Echocardiography Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day*)
Screening	Visit 1		Screening	Up to -1	< 1
DB	Baseline/Visit 2	Day 1	Baseline	1	<=1
	Visit 5	Week 12	Week 12	84	[2 to 126]
	Visit 7	Week 24	Week 24	168	[127 to 252]
	Visit 9	Week 48	Week 48	336	[253 to 420]

*Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in the PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).
DB = Double-blind.

Table 7: Scheduled Visits and Analysis Visit Windows for Hematology, Chemistry and Electrocardiogram (ECG) Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day*)
Screening	Visit 1		Screening	Up to -1	< 1
DB	Baseline/Visit 2	Day 1	Baseline	1	[−42 to 1]
	Visit 3	Week 4	Week 4	28	[2 to 56]
	Visit 5	Week 12	Week 12	84	[57 to 98]
	Visit 6	Week 16	Week 16	112	[99 to 140]
	Visit 7	Week 24	Week 24	168	[141 to 210]
	Visit 8	Week 36	Week 36	252	[211 to 294]
	Visit 9	Week 48	Week 48	336	[295 to 378]
	Visit 10	Week 60	Week 60	420	[379 to 462]
	...				
	Visit x	Week n	Week n	n*7	[n*7 - 41 to n*7 + 42]

*Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in the PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).

Table 8: Scheduled Visits and Analysis Visit Windows for Palatability and Acceptability Assessments

Analysis Period	Scheduled Visit Number	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day*)
DB	Visit 3	Week 4	Week 4	28	[2 to 56]
	Visit 5	Week 12	Week 12	84	[57 to 112]

*Relative to Study Day 1. Visit windows for analyses are wider than the assessment windows specified in the protocol. The visit windows will be applied to all collected data including scheduled, unscheduled and visits in the PTOP visits. PTOP flag will be included in the analysis datasets (ADaM).
DB = Double-blind.

4.1.2. Pooling Algorithm for Centers

Randomization is not stratified by center due to the small number of participants expected at each center.

Where summaries or analysis are by region, the pooling of centers will be applied considering geographical areas as defined in the PAH adult Phase 3 GRIPHON study (Clinical Study Report AC-065A302 (GRIPHON) 2014). The following geographical areas are considered:

- Asia
- Eastern Europe
- Latin America
- North America
- Western Europe.

A list of countries included in each region will be presented in the DPS Part 1.

4.1.3. Double-Blind Study Intervention Start Date

For each participant, the DB start date (DBSD) is the date of the first dose of study intervention received. It is derived as the start date of the first interval, in chronological order, recorded in the "Study Drug Administration for Selexipag or Placebo - Double Blind Treatment" eCRF form.

If missing or incomplete, the rules in Section 4.1.12 will be applied.

4.1.4. Cut-off Date for Analyses

Details on data cut-offs applied are documented in the database release plan.

4.1.5. Double-Blind Study Intervention End Date

For each participant, the end of DB study intervention (DBED) is the date when the last dose of study intervention was received in a DB fashion. It is derived as the end date of the last interval, in chronological order, recorded in the "Study Drug Administration for Selexipag or Placebo - Double Blind Treatment" eCRF form.

If missing or incomplete, the rules in Section 4.1.12 will be applied.

4.1.6. End of Double-Blind Treatment Period

At the study level, the EDBT was announced by the sponsor after the results of Analysis 2 (see Section 1.2.1 and Section 1.2.2) were available, at which point all ongoing participants were requested to return for their end of DB assessment. For participants entering the OLEP, the participants EDBT (morning) is expected to occur on the same day as the start of OL intervention (evening). Participants end of DB assessments are performed in the morning prior to initiation of OL intervention.

4.1.7. Bosentan as Study Rescue Treatment

Participants not treated with any endothelin receptor antagonist (ERA) (eg, bosentan, macitentan or ambrisentan) at study randomization and with PAH-progression may be eligible for rescue treatment with bosentan provided by the sponsor in the context of the study. Its administration is captured in the eCRF.

4.1.7.1. Bosentan Start Date

The start of bosentan as a study rescue treatment is determined for applicable participants as the date when the first dose of bosentan as study rescue treatment was administered based on the start date of the first interval, in chronological order, recorded in the "Study Drug Administration for Bosentan - Double Blind Treatment" eCRF form.

If the start date is incomplete or missing, the rules in Section 4.1.12 will be applied.

4.1.7.2. Bosentan End Date

The end of bosentan as a study rescue treatment is determined for applicable participants as the date when the last dose of bosentan as a study rescue treatment was administered based on the end

date of the last interval, in chronological order, recorded in the "Study Drug Administration for Bosentan - Double Blind Treatment" eCRF form.

If the end date is incomplete or missing, the rules in Section 4.1.12 will be applied.

4.1.8. Study Day and Relative Day

Visit 2 is the date of randomization and usually also the date of the first study intervention administration (in the evening). In general, in the DB treatment period, for baseline characteristics, as well as efficacy endpoints the Study Day 1 or Day 1 refers to the date of randomization; while for medical history, previous and concomitant medications, exposure, and safety endpoints the Study Day 1 or Day 1 refers to the date of the first study intervention administration. If the date of randomization and the date of the first study intervention administration are different, the study day will not be the same for all endpoints.

All efficacy and safety assessments at all visits will be assigned a study day relative to Study Day 1.

Study day or relative day for an event/assessment visit on or after the respective Study Day 1 (≥ date of Study Day 1) is defined as:

- Event date/Assessment Visit date - (Study Day 1 date) + 1
- Study day or relative day for an event/assessment visit prior to the respective Study Day 1 (< date of Study Day 1) is defined as:
- Event/Assessment Visit date - (date of Study Day 1).

There is no 'Day 0'.

4.1.9. Baseline

The baseline value is the last non-missing assessment obtained before or on the DBSD (see Section 4.1.3). If unscheduled/re-test visits are performed on the day of study intervention start, the non-missing value of the last unscheduled/re-test visit on study intervention start date is considered as baseline. In cases where more than one assessment is available, the worst value will be considered for categorical variables (higher or lower value, depending on the parameter: an explicative table will be included in the DPS Part 1), while the average value will be calculated for continuous variables.

4.1.10. Last Contact Date in the DB Period

The last contact date in the DB period is defined as the latest of the following non-missing dates:

- Adverse Event (AE) onset/resolution date
- Concomitant medication start/end date
- Hospitalization admission/discharge date
- Death date

- Any event date confirmed by the CEC
- Clinical Worsening Event date (as recorded on the 'Clinical Worsening of PAH' eCRF)
- DB study intervention start/end dates, OL start date (for those participants entering the OLEP)
- Disposition dates (including Survival Follow-up contact date)
- Any visit-based assessments such as, but not limited to: ECG, laboratory, vital signs, 6MWT and questionnaires.

In case the last contact date derived above is after the participant's initiation of OL intervention date, the last contact date will be imputed with the initiation date of OL intervention.

4.1.11. Timeframe of interest for efficacy and safety endpoints

For each participant, the start of OL selexipag (OL Day 1) is the date when the first dose of OL selexipag was received in the OLEP. It is derived as the start date of the first interval, in chronological order, recorded in the "Study Drug Administration for Selexipag – Open Label Treatment" eCRF form.

If incomplete, the rules in Section 4.1.12 will be applied.

For specific efficacy and safety endpoints, the following naming convention and rules will be applied:

- DBED + X days/OL Day 1 =
  - min (DBED + X days, OL Day 1), for participants who enter the OLEP
  - DBED + X days, for participants who do not enter the OLEP.

4.1.12. Imputation Rules for Missing or Incomplete Dates

The following imputation rules are used for missing or partially collected dates that are key for statistical analysis conventions:

Type of Date	Date Incomplete	Date Missing
DBED*	Earliest date between the following: • Last day of the month if only day is missing, 31 December if day and month missing • last contact date • date of death (if applicable)	Use the earliest date between the: • last contact date • date of death (if applicable)
DBSD	• If day is missing, replace with day of randomization date. In case the day of randomization is in a previous month, replace the day with 1. • If day and month are missing replace the whole date with the randomization date.	Randomization date.
Bosentan as study rescue treatment: treatment start date*	• 15th day of the month if only day is missing, 31 December if day and month missing.	No imputation, it is considered as not taken.

Type of Date	Date Incomplete	Date Missing
Bosentan as study rescue treatment: treatment end date*	• Last day of the month if only day is missing, 31 December if day and month missing.	If bosentan rescue treatment start date exists, it is set equal to EDBT date.
AE resolution date*	• Last day of the month if only day is missing, 31 December if day and month missing.	No imputation, the AE is considered as ongoing in the analysis.
AE onset date*	• If the end date of the AE is not before the DBSD and if the DBSD falls in the range of possible dates, it is the DBSD. • In all the other cases, it is the first day of the month or 1 January.	The earlier of the end date of the AE and DBSD.
Hospitalization admission date	• If the onset date of the AE leading to hospitalization falls in the same month as the hospitalization, it is the start date of the AE. • In all other cases, it is the first day of the month or 1 January.	The start date of the AE leading to hospitalization.
Hospitalization discharge date	• Last day of the month if only day is missing, 31 December if day and month missing, unless death date or min(last contact date in DB, OL Day 1) is sooner.	The earlier of death date or min(last contact date in DB, OL Day 1).
Previous/ concomitant medication start date	• If incomplete, it will be imputed to the lower limit, ie, the minimum of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month. If the day and month are missing, the lower limit refers to 1 January of the given year. • In case "Started prior to first study treatment intake" is no, and if the DBSD falls in the range of possible dates, the DBSD is used.	• No replacement, the medication is considered to have started before the DBSD if "Started prior to first study treatment intake" flag is yes or the medication end date is before the DBSD. • Otherwise, the medication is considered to have started after the DBSD.
First PAH symptoms date	• If the day is missing, the lowest limit is the first day of the given month. If the day and month are missing, the lower limit refers to 1 January of the given year.	No replacement, it will not be considered in the descriptive statistics.
Previous/ concomitant medication end date*	• If incomplete, it will be imputed to the upper limit, ie, the maximum of a possible date. For example, if the day is missing, the upper limit is the last day of the given month. If the day and month are missing, the upper limit refers to 31 December of the given year.	No replacement (considered ongoing).
Date of PAH diagnosis	• Day missing: 15th of the month. • Day and month missing: 30 June. • If the resulting date is later than the date of randomization and the lower limit is not later than the randomization date, then the date is substituted with the date of randomization.	No replacement.
Date of death (if applicable)	• Day missing: 15th of the month (unless later known alive date/assessment date is in the same month then will be last known alive date/assessment date +1). • Day and month missing: no replacement.	No replacement.

Type of Date	Date Incomplete	Date Missing
Date of initiation of OL intervention (OL Day 1)	• If day is missing, replace with day of DBED. In case the day of DBED is in a previous month, replace the day with 1. • If day and month are missing replace the whole date with the DBED date.	No replacement. Participant considered as not entered into OL.

*For participants who entered the OLEP, the upper limit should not exceed OL Day 1.

4.1.13. End of Study Date

The 'End of Study (EOS) date' is defined as the date on the 'Trial Disposition (Completion/ Discontinuation)' eCRF page.

The EOS is intended to occur at the end of OLEP, however for participants who do not enter the OLEP or PTOP (see protocol Section 4.1), the EOS date should coincide with the follow-up call 30 days after DBED.

If this date is missing and the participant has completed or prematurely discontinued the study, the last contact date is considered as the EOS date.

4.2. Primary Endpoint Analysis

4.2.1. Main Analysis

4.2.1.1. Definition of Endpoint

The primary efficacy variable is the time from randomization to the first CEC-confirmed disease progression event occurring between the date of randomization until DBED + 7 days/OL Day 1. For missing or incomplete DBED dates, imputation rules are defined in Section 4.1.12.

Disease progression is a composite event, and an independent CEC will adjudicate, in a blinded fashion, all potential disease progression events reported by investigators to determine the components of the event, the relationship of hospitalization with PAH as well as the event onset date. Time from randomization to the first disease progression will be expressed in days and calculated as the onset date of the first CEC-confirmed disease progression minus date of randomization + 1.

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

- Death (all causes)
- Atrial septostomy or Potts' anastomosis, or registration on lung transplant list
- Hospitalization due to worsening PAH[§]
- Clinical worsening[*] of PAH defined as:
- Need for, or initiation of new PAH-specific therapy[#] or i.v. diuretics or continuous oxygen use AND at least one of the following:
  - Worsening in WHO FC, or

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

[§]excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (eg, pneumonia).
[*]Worsening from baseline.
[#]eg, ERA, PDE-5 inhibitor, prostacyclin or its analogues, prostacyclin (IP)-receptor agonist, soluble guanylate cyclase stimulator.

4.2.1.2. Estimand

Primary Trial Objective:

To evaluate whether the addition of selexipag to SoC treatment delays disease progression in children with PAH in comparison to the addition of placebo to SoC treatment.

Estimand scientific question of interest:

What are the effects of selexipag versus placebo added to SoC on time to the first CEC-confirmed event of disease progression in children aged 2 to <18 years with PAH diagnosis confirmed by historical RHC?

Main estimand

The main estimand is described according to the following attributes:

Study Intervention:

- Selexipag
- Placebo

Population: Pediatric participants with PAH, aged between 2 and <18 years.

Variable: Time (in days) from randomization to the first CEC-confirmed disease progression event up to DBED + 7 days/OL Day 1.

Summary measure (Population-level summary): The hazard ratio (HR) of selexipag versus placebo.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Name of Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason without experiencing a CEC-confirmed disease progression	**While on treatment strategy:** the time to disease progression will be right censored at DBED + 7 days/OL Day 1.

Withdrawal of consent/Lost to follow-up without experiencing a CEC-confirmed disease progression	**While on treatment strategy:** the time to disease progression will be right censored at the earlier of date of last contact/DBED + 7 days/OL Day 1.
Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) while on DB study intervention and before a CEC-confirmed primary event occurrence	**Treatment policy strategy:** CEC-confirmed disease progression events will be considered irrespective of whether occurring after initiation or escalation in PAH-specific therapy.

4.2.1.3. Analysis Methods

Assumptions:

- Non-informative censoring assumed for all types of censoring.
- Distinct baseline hazard for each stratum included in the analysis (WHO FC at randomization [II, III] and by the number of PAH-specific therapies at randomization (monotherapy [1], combination therapy [≥2])), with a common proportional HR across strata.

Handling of censoring

Participants who do not experience any CEC-confirmed progression events during the DB will have their time to disease progression event censored at the earliest of the following times:

- DB study intervention discontinuation + 7 days/OL Day 1 (ie, DBED + 7 days/OL Day 1); for missing or incomplete DBED date or incomplete OL Day 1, imputation rules will be applied as defined in Section 4.1.12
- Last contact date (see Section 4.1.10).

Main Estimator for Main Estimand

The primary analysis will be performed on participants of the FAS, according to the randomized intervention group.

Time to disease progression will be descriptively summarized with KM estimates and 2-sided 95% CIs for probability of no event for each intervention group, overall and by age cohort and displayed in both a graphical and a tabular form. In addition, a Cox proportional hazards model will be used to estimate the HR of selexipag versus placebo. This will be presented together with 2-sided 95% CIs. In addition to the intervention group the model will have additional terms corresponding to the IWRS stratification factors at randomization: WHO FC at randomization (II, III) and the number of PAH-specific therapies (monotherapy [1], combination therapy [≥2]) at randomization.

The number of participants who experienced intercurrent events prior to DBED will also be summarized for each intervention group, overall and by age cohort.

A listing of time to first CEC-confirmed disease progression events will be provided on the FAS.

A listing of all CEC-confirmed disease progression events will also be provided on the FAS (where the first CEC-confirmed disease progression events will be flagged).

In addition, a listing of the investigators assessed disease progression events will also be provided on the FAS. CEC-confirmed events will be highlighted in the listing.

If more than 5% of participants are mis-stratified, ie, stratification factors as collected on the eCRF do not match those entered in IWRS (for number of PAH-specific therapies at randomization or WHO FC at randomization), the primary analysis will be repeated using the stratification variables as recorded on the eCRF.

4.2.1.4. Sensitivity Analyses

Not applicable.

4.2.1.5. Subgroup Analyses

Treatment effect estimates (HR) and the corresponding 2-sided 95% CI for the different levels of each demographic and baseline characteristics in Table 11 along with the number and percentage of participants with events, will be presented as a forest plot.

4.2.2. Supplementary Analyses

In support of the primary efficacy analysis, a supplementary analysis will be performed for the following supplementary estimand:

Supplementary Estimand

The supplementary estimand differs from the main estimand by following a treatment policy strategy for premature DB study intervention discontinuation.

Study intervention, population, and summary measure (population-level summary) are as described for the main estimand (Section 4.2.1.2). The analysis will be conducted on the FAS.

Variable:

Time to the first CEC-confirmed disease progression event occurring up to the end of the DB period/OL Day 1 will be derived as the time in days from randomization to the first CEC-confirmed disease progression event experienced by a participant.

Participants who do not experience any CEC-confirmed disease progression event will have their time to event censored at the earliest of the following times:

- Date of premature study discontinuation
- Last contact date.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Name of Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason without experiencing a CEC-confirmed disease progression	**Treatment policy strategy**: Adjudicated CEC-progression events will be considered irrespective of whether occurring on or off intervention in the DB treatment period.
Withdrawal of consent/Lost to follow-up without experiencing a CEC-confirmed disease progression	**Treatment policy strategy:** the time to CEC-confirmed disease progression will be right censored at the date of last contact.

Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) while on DB study intervention and before a CEC-confirmed primary event occurrence	**Treatment policy strategy:** CEC-confirmed disease progression events will be considered irrespective of whether occurring after initiation or escalation in PAH-specific therapy.

4.3. Secondary Efficacy Endpoint Analysis

4.3.1. NT-proBNP

4.3.1.1. Main Analysis

4.3.1.1.1. Definition of Endpoint

This endpoint is defined as the change from baseline to Week 24 in the central laboratory NT-proBNP (ng/L) value, expressed as the $\log_2$-transformed ratio of the Week 24 NT-proBNP value over the baseline value:

- $\log_2$ (Week 24 NT-proBNP / Baseline NT-proBNP)

Clinically, a reduction from baseline in NT-proBNP (ratio < 1) is considered an improvement.

4.3.1.1.2. Estimand

Secondary Trial Objective

To evaluate whether the addition of selexipag to SoC improves NT-proBNP values in children with PAH in comparison to placebo.

Estimand scientific question of interest:

What are the effects of selexipag versus placebo added to SoC on NT-proBNP change from baseline to Week 24 in children aged 2 to <18 years with PAH with their diagnosis confirmed by historical RHC?

Main estimand

The main estimand is described according to the following attributes:

Study Intervention:

- Selexipag
- Placebo

Population: Pediatric participants with PAH, aged between 2 and <18 years.

Variable: Change in NT-proBNP from baseline to Week 24 expressed as $\log_2$(Week 24/Baseline).

Summary measure (Population-level summary): The geometric mean ratio of selexipag versus placebo.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Name of Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason and without NT-proBNP assessment at Week 24	**Treatment policy strategy:** the missing NT-proBNP value at Week 24 will be imputed and utilized in the analysis.
Withdrawal of consent/Lost to follow-up and without NT-proBNP assessment at Week 24	
Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) prior to NT-proBNP assessment at Week 24	**Treatment policy strategy:** The NT-proBNP value at week 24 will be considered irrespective of whether occurring after initiation or escalation in PAH-specific therapy.

Handling of missing data

Multiple imputation (MI) methodology (O'Kelly 2014) will be applied to impute all missing NT-proBNP values under a missing at random (MAR) assumption, with a modification for values missing due to participants in the selexipag intervention group discontinuing the study intervention due to a disease progression. The modification assumes that the trajectory for participants in the selexipag group with CEC-confirmed disease progression prior to Week 24 and without NT-proBNP assessment at Week 24 is similar to that of the placebo participants, whereas the remaining participants who have dropped out are imputed assuming MAR.

This allows an assessment of a deviation from the MAR assumption for participants who discontinue study intervention due to a disease progression and assume these missing values are missing not at random (MNAR).

Imputation will be done in two steps, based on $\log_2$ transformed values of NT-proBNP. First, missing intermittent Week 16 values are imputed based on a Markov Chain Monte Carlo (MCMC) using a monotone regression method (using PROC MI in SAS) to create 100 partially completed datasets with monotone missing data pattern. The intervention group, $\log_2$ transformed baseline NT-proBNP value and IWRS randomization stratification variables factors are included in the imputation model.

Next, the missing value at Week 24 will be imputed using a sequential regression method (using MONOTONE REG option of SAS PROC MI).

The MNAR imputation is achieved by only using appropriate data to impute missing analysis values at Week 16 and Week 24. For example, to impute missing values at time t for participants in the selexipag group, who dropped out due to disease progression, include only placebo observations up to and including time t, plus observations from participants in the selexipag group who terminated study intervention because of a disease progression up to and including time t-1. This will be done for Week 16 and Week 24, one at a time using observed data, and missing values that have been imputed at the previous step. The intervention group will not be included in the imputation model for this step. Placebo missing observations, and selexipag observations that are

missing for any other reason, are imputed assuming MAR and follow the pattern in each intervention group, respectively. A seed of 260123 will be used for both steps.

Each of the 100 imputed datasets will be analyzed as described in Section 4.3.1.1.3 using observed and imputed data and the results will be aggregated (Rubin 1987) using the SAS procedure PROC MIANALYZE.

4.3.1.1.3. Analysis Methods

Main Estimator:

NT-proBNP data will be analyzed using an ANCOVA model on the $\log_2$ transformed NT-proBNP (Week 24/Baseline) and conducted on the FAS. Model covariates will include intervention group, IWRS randomization stratification factors [WHO FC (II, III) at randomization and PAH-specific therapy at randomization (monotherapy [1], combination therapy [≥2])] and the $\log_2$ transformed baseline NT-proBNP value.

For each intervention group, overall and by age cohort, the geometric mean and the corresponding associated 2-sided 95% CI will be presented. The treatment effect at Week 24 expressed as the ratio of geometric means and corresponding associated 95% CI will be estimated based on the same model, derived by applying the back transformation (2^x) of model outcomes used for the ratios of Week 24 to baseline. Superiority of the selexipag group will be evaluated based on p-value for between-intervention difference in $\log_2$(Week 24/Baseline) tested at an overall 2-sided 5% significance level.

Descriptive statistics for observed absolute values at baseline and Week 24, absolute change from baseline values at Week 24, and the geometric mean of Week 24/baseline ratio (derived by applying the back transformation (2^x) to the mean of $\log_2$(Week 24/Baseline)) and corresponding associated 2-sided 95% CI will be provided by intervention group overall.

Change from baseline will be calculated as:

NT-proBNP value at Week 24 − NT-proBNP value at baseline.

From the ANCOVA model, ratio of Week 24 to baseline NT-proBNP will be summarized by treatment group using covariate-adjusted geometric means and corresponding 2-sided 95% CI. The between-group ratio of geometric means with corresponding 2-sided 95% CI and p-value will be displayed as the placebo-corrected treatment effect.

The number of participants with missing values for NT-proBNP (ng/L) at Week 16 and Week 24 will also be provided by intervention group, overall.

The number of participants who experienced intercurrent events prior to NT-proBNP assessment at Week 24 will also be summarized for each intervention group, overall.

A listing of observed NT-proBNP values up to Week 24 and change from baseline to Week 24 will also be provided.

4.3.1.1.4. Sensitivity Analysis

Not applicable.

4.3.1.1.5. Subgroup Analyses

Treatment effect estimates and the corresponding 2-sided 95% CI for the different levels of each demographic and baseline characteristics in Table 11 will be presented as a forest plot for the FAS.

4.3.1.2. Supplementary Analyses

In support of the main analysis of the secondary endpoint NT-proBNP, the main analysis described Section 4.3.1.1.3 will be repeated for the PPS, by intervention group, overall.

In addition, the following supplementary analysis will be performed:

Supplementary Analysis A

Study intervention, population, intercurrent events, and strategies are as described for the main estimand (Section 4.3.1.1.2).

Variable: CCI [redacted]

Summary measure (Population-level summary): Odds ratio (OR) of selexipag versus placebo.

The CCI [redacted] responder variable will be analyzed using logistic regression analysis, including intervention group, IWRS randomization stratification [WHO FC (II,III) at randomization, PAH-specific therapy at randomization (monotherapy [1], combination therapy [⩾2]), age, sex, and severe impaired renal function (Yes, No) (if there are at least 20% participants with severely impaired renal function – defined as estimated creatinine clearance <30 mL/min or serum creatinine >221 µmol/L at any time during the DB treatment period) as covariates.

The OR for the treatment effect will be displayed together with 2-sided 95% CI and descriptive p-value.

The number of participants who experienced intercurrent events prior to NT-proBNP assessment at Week 24 will be summarized as described for the main estimand.

Handling of missing data

Missing data will be handled as described for the main estimand (Section 4.3.1.1.2). Each of the 100 imputed datasets will be analyzed using observed and imputed data, and results will be aggregated (Rubin 1987) using the SAS procedure PROC MIANALYZE.

4.3.2. Time to first CEC-confirmed hospitalization or death due to PAH

4.3.2.1. Definition of Endpoint

The endpoint of first CEC-confirmed Death or Hospitalization (D/H) due to PAH event is defined as the earlier of:

- Death due to PAH

  or

- PAH-related hospitalization

occurring from randomization until DBED + 7 days/OL Day 1.

4.3.2.2. Estimand

Secondary Trial Objective

To evaluate whether the addition of selexipag to SoC prolongs the time to death or hospitalization due to PAH (adjudicated by an independent CEC) compared to placebo.

Estimand scientific question of interest:

What is the effect of selexipag versus placebo on the time to first CEC-confirmed D/H due to PAH in children aged 2 to <18 years with PAH with diagnosis confirmed by historical RHC?

Main estimand

The main estimand is described according to the following attributes:

Study intervention, population, and summary measure (population-level summary) are as described for the primary estimand of the primary endpoint in Section 4.2.1.2.

Variable: time (in days) to the first CEC-confirmed D/H due to PAH event from randomization up to DBED + 7 days/OL Day 1.

It is calculated as the onset date of the first occurrence of CEC-confirmed D/H due to PAH minus date of randomization + 1 day or, for censored participants, as censoring date minus date of randomization + 1 day.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason without experiencing a CEC-confirmed D/H due to PAH	**While on treatment strategy:** the time to the specified event will be right censored at DBED + 7 days/OL Day 1.
Withdrawal of consent/Lost to follow-up without experiencing a CEC-confirmed D/H due to PAH	**While on treatment strategy:** the time to the specified event will be right censored at the earlier of date of last contact/DBED + 7 days.
Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) while on DB study intervention and before a CEC-confirmed D/H due to PAH	**Treatment policy strategy:** the time to the specified event will be considered irrespective of whether occurring after initiation or escalation in PAH-specific therapy.
Death not due to PAH up to DB study intervention discontinuation + 7 days	**While alive strategy:** the time to the specified event will be right censored at the date of death not due to PAH.
Death due to unknown cause up to DB study intervention discontinuation + 7 days	**While alive strategy:** the time to the specified event will be right censored at the date of death due to unknown cause.

4.3.2.3. Analysis Methods

4.3.2.3.1. Main Analysis

Time to first CEC-confirmed D/H due to PAH event (see Section 4.3.2) will be derived as the time in days from randomization to the first CEC-confirmed D/H due to PAH event experienced by a participant, including events that occurred prior to DBED + 7 days/OL Day 1.

Participants who do not experience any CEC-confirmed D/H due to PAH event will have their time to event censored at the earliest of the following times:

- Study intervention discontinuation + 7 days/OL Day 1 (ie, DBED + 7 days/OL Day 1)
- Last contact date
- Date of death in the event of death due to non-PAH cause or Unknown cause (as adjudicated by the CEC).

Assumptions and main estimator are as described for the primary endpoint in Section 4.2.1.3. The analysis will be conducted on the FAS.

Time to first CEC-confirmed D/H due to PAH event will be descriptively summarized with KM estimates and 2-sided 95% CIs for probability of no event for each intervention group, overall and by age cohort and displayed in both a graphical and a tabular form.

In addition, a Cox proportional hazards model will be used to estimate the HR of selexipag versus placebo. This will be presented together with 2-sided 95% CIs. In addition to the intervention group the model will have additional terms corresponding to the IWRS stratification factors at randomization: WHO FC at randomization (II, III) and the number of PAH-specific therapies (monotherapy [1], combination therapy [≥2]) at randomization.

The number of participants who experienced intercurrent events prior to DBED will also be summarized for each intervention group overall.

A listing of time to first CEC-confirmed D/H due to PAH events will be provided on the FAS.

A listing of all CEC-confirmed D/H due to PAH events will also be provided on the FAS, where the first CEC-confirmed D/H due to PAH events will be flagged. Events occurring after DBED + 7 days will also be flagged.

4.4. Tertiary/Exploratory Analysis

4.4.1. Time to Death (All Causes)

4.4.1.1. Definition of Endpoint

The exploratory endpoint of time to all-cause death is defined as:

- Time to death occurring between randomization and the end of the DB period
- All-cause death, including all deaths occurring during the DB period regardless of potential discontinuation of study intervention, or initiation or escalation in PAH medication. The date of death will be used in the analysis.

4.4.1.2. Estimand

Exploratory trial objective

To assess the effect on prolongation of the time to death for selexipag compared to placebo.

Estimand scientific question of interest

What is the effect of selexipag versus placebo on time to all-cause death in children aged 2 to <18 years with PAH with their diagnosis confirmed by historical RHC?

Main estimand

The main estimand for time to all-cause death event will follow a "treatment policy" strategy for intercurrent events. Therefore, events of death will be considered regardless of potential discontinuation of study intervention or initiation of PAH-specific therapy.

The main estimand is described according to the following attributes:

Study intervention, population, and summary measure (population-level summary) are as described for the main estimand of the primary endpoint in Section 4.2.1.2.

Variable: time (in days) to all-cause death up to the end of the DB period.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason without a death event	**Treatment policy:** Time to all-cause death events will be considered irrespective of whether occurring on or off intervention.
Withdrawal of consent / Lost to follow-up and without a death event	**Treatment policy:** Time to all-cause death events will be right censored at the date of last contact in the DB period.
Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) while on DB study intervention and before death event	**Treatment policy:** Time to all-cause death events will be considered irrespective of whether occurring after initiation or escalation in PAH-specific therapy.

4.4.1.3. Analysis Methods

4.4.1.3.1. Main analysis

Participants still alive at the end of the DB period will have their time to death right-censored at the last contact date in the DB period (Section 4.1.10).

Time from randomization to death will be expressed in days and calculated as the date of death minus date of randomization + 1 day or, for censored participants, as censoring date minus date of randomization + 1 day.

The analyses will be conducted using KM estimates of events over time. KM estimates will be calculated with 2-sided 95% CIs at relevant timepoints (6 monthly intervals) for each intervention group, overall and displayed in both a graphical (where the number of participants at risk is at least

10% of the total number of participants in the analysis set) and tabular form. Cox proportional hazards model will be used to estimate the HR of selexipag versus placebo. This will be presented together with 2-sided 95% CIs. In addition to the intervention group the model will have additional terms corresponding to the IWRS stratification factors at randomization: WHO FC at randomization (II, III) and the number of PAH-specific therapies (monotherapy [1], combination therapy [≥2]) at randomization.

The number of participants who experienced intercurrent events prior to death (all causes) will also be summarized for each intervention group, overall.

A listing of all-cause death events that occurred on or after Study Day 1 will be provided on the FAS.

4.4.2. Time to CEC-confirmed Hospitalization due to PAH

4.4.2.1. Definition of Endpoint

The exploratory endpoint of time to first CEC-confirmed hospitalization due to PAH event is defined as an unplanned hospitalization due to PAH occurring from randomization until DBED + 7 days/OL Day 1.

4.4.2.2. Estimand

Exploratory trial objective

To assess the effect on prolongation of the time to first hospitalization due to PAH (adjudicated by an independent CEC) for selexipag compared to placebo.

Estimand scientific question of interest

What is the effect of selexipag versus placebo on time to first hospitalization due to PAH in children aged 2 to <18 years with PAH with their diagnosis confirmed by historical RHC?

Main estimand

The estimand is described according to the following attributes:

Study intervention, population, and summary measure (population-level summary) are as described for the main estimand of the primary endpoint in Section 4.2.1.2.

Variable: time (in days) to first CEC-confirmed hospitalization due to PAH event up to DBED + 7 days/OL Day 1.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Name of Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason without experiencing a CEC-confirmed hospitalization due to PAH	**While on treatment strategy:** the time to first hospitalization due to PAH will be right censored at DBED + 7 days/OL Day 1.

Withdrawal of consent/Lost to follow-up without experiencing a CEC-confirmed hospitalization due to PAH	**While on treatment strategy:** the time to first hospitalization due to PAH will be right censored at the earlier of date of last contact/ DBED + 7 days/OL Day 1.
Death up to DB study intervention discontinuation + 7 days	**While alive strategy:** the time to first hospitalization due to PAH will be right censored at the date of death.
Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) while on DB study intervention and before a CEC-confirmed hospitalization due to PAH	**Treatment policy strategy:** CEC-confirmed hospitalization due to PAH will be considered irrespective of whether occurring after initiation or escalation in PAH-specific therapy.

4.4.2.3. Analysis Methods

4.4.2.3.1. Main analysis

Participants without an event at or after DBED + 7 days/OL Day 1 will have their time to first hospitalization right-censored at the earliest of the following times:

- Study intervention discontinuation + 7 days/OL Day 1 (ie, DBED + 7 days/OL Day 1)
- Last contact date (see Section 4.1.10).

Time from randomization to first CEC-confirmed hospitalization due to PAH will be expressed in days and calculated as the date of the first CEC-confirmed hospitalization for PAH experienced by a participant minus date of randomization + 1 day or, for censored participants, as censoring date minus date of randomization + 1 day.

The analyses will be conducted as described in Section 4.4.1.3.1.

A listing of time to first CEC-confirmed hospitalization due to PAH will be provided on the FAS.

A listing of all CEC-confirmed hospitalizations due to PAH events that occurred on or after Study Day 1 will also be provided on the FAS. Events occurring after DBED + 7 days will be flagged.

4.4.3. Time to CEC-confirmed Death due to PAH

4.4.3.1. Definition of Endpoint

The exploratory endpoint of time to CEC-confirmed death due to PAH event is defined as:

Death due to PAH occurring from randomization until DBED + 7 days/OL Day 1.

4.4.3.2. Estimand

Exploratory trial objective

To assess the effect on prolongation of the time to death due to PAH (adjudicated by an independent CEC) for selexipag compared to placebo.

Estimand scientific question of interest

What is the effect of selexipag versus placebo on time to death due to PAH in children aged 2 to <18 years with PAH with their diagnosis confirmed by RHC?

Main estimand

The estimand is described according to the following attributes:

Study intervention, population, summary measure (population-level summary), and intercurrent events and their corresponding strategies are as described for the main estimand of the secondary endpoint in Section 4.3.2.2.

Variable: time (in days) to CEC-confirmed death due to PAH event up to DBED + 7 days/OL Day 1.

4.4.3.3. Analysis Methods

4.4.3.3.1. Main analysis

Participants still alive at or after DBED + 7 days/OL Day 1 will have their time to death right-censored at the earliest of the following times:

- Study intervention discontinuation + 7 days/OL Day 1 (ie, DBED + 7 days/OL Day 1)
- Last contact date (see Section 4.1.10)
- Date of death in the event of death due to non-PAH cause or Unknown cause (as adjudicated by the CEC).

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

The analyses will be conducted as described in Section 4.4.1.3.1.

A listing of time to CEC-confirmed death due to PAH will be provided on the FAS.

A listing of CEC-confirmed death due to PAH events that occurred on or after Study Day 1 will also be provided on the FAS. Events occurring after DBED + 7 days will be flagged.

4.4.4. Time to Clinical Worsening

4.4.4.1. Definition of Endpoint

The exploratory endpoint of time to clinical worsening is defined as the time from randomization to the first clinical worsening event occurring between the date of randomization until DBED + 7 days/OL Day 1.

Clinical worsening is a composite event. The events to be considered for the first clinical worsening are (adapted from the Committee for Medicinal Products for Human Use (CHMP) definition [EMEA 2008]):

- Death (all causes)
- Non-planned PAH-related hospitalization

- PAH-related deterioration identified by at least one of the below criteria:
  - Increase in WHO FC,
  - Deterioration in exercise testing (15% decrease from baseline in 6MWD),
  - New or worsening signs or symptoms of right-side heart failure.

To determine a clinical worsening event, all hospitalizations captured in the eCRF will be considered (where 'Was hospitalization due to PAH worsening?' on the Adverse Events/Serious AEs eCRF is indicated as Yes). In addition, all signs/symptoms on the 'Signs and Symptoms of PAH - Post Baseline' eCRF page indicated as 'New occurrence' or 'Worsening 'will be considered when determining new or worsening signs or symptoms of right-side heart failure.

Deterioration in exercise testing can only be assessed in those participants from ≥6 to <18 years of age. 6MWD is not determined for participants outside of this age range.

4.4.4.2. Estimand

Exploratory Trial Objective:

To assess whether the addition of selexipag to SoC treatment delays clinical worsening in children with PAH in comparison to placebo.

Estimand scientific question of interest:

What are the effects of selexipag versus placebo on time to the first event of clinical worsening in children aged 2 to <18 years with PAH with diagnosis confirmed by historical RHC?

Main estimand

The main estimand is described according to the following attributes:

Study intervention, population, and summary measure (population-level summary) are as described for the main estimand of the primary endpoint in Section 4.2.1.2.

Variable: Time (in days) from randomization to the first clinical worsening event up to DBED + 7 days/OL Day 1.

Intercurrent Events and their corresponding strategies:

The following intercurrent events and strategies are considered:

Intercurrent event	Strategy for Addressing Intercurrent Events and Its Description
Premature DB study intervention discontinuation for any reason without experiencing a clinical worsening	**While on treatment strategy:** the time to event will be right censored at DBED + 7 days/OL Day 1.
Withdrawal of consent/Lost to follow-up without experiencing a clinical worsening	**While on treatment strategy:** the time to clinical worsening will be right censored at the earlier of date of last contact/DBED + 7 days/OL Day 1.
Participants receiving new PAH-specific therapy (see Section 6.8 Appendix 8) while on DB study intervention and before an event occurrence	**Treatment policy:** Clinical worsening events will be considered irrespective of whether occurring after initiation or escalation in PAH medication.

4.4.4.3. Analysis Methods

4.4.4.3.1. Main Analysis

Time from randomization to first clinical worsening will be expressed in days and calculated as the onset date of the first clinical worsening event minus date of randomization + 1 day or, for censored participants, as censoring date minus date of randomization + 1 day.

Participants without an event at or after DBED + 7 days/OL Day 1 will have their time to clinical worsening right-censored at the earliest of the following times:

- Study intervention discontinuation + 7 days/OL Day 1 (ie, DBED + 7 days/OL Day 1)
- Last contact date (see Section 4.1.10).

The analyses will be conducted as described in Section 4.4.1.3.1.

The number (and percentage) of participants reporting each component will be summarized for the first clinical worsening event for each intervention group, overall. The number (and percentage) of participants reporting the first of each type of component will also be summarized.

These components, evaluated by the investigator for assessment of the clinical worsening and recorded in the eCRF, will be listed on the FAS:

- time to first clinical worsening event
- all clinical worsening events that occurred on or after Study Day 1 (events occurring after DBED + 7 days will be flagged).

4.4.5. WHO FC

The WHO Functional Classification contains 4 levels of functioning: Class I (no limitations of activity), Class II (slight limitations), Class III (marked limitations) and Class IV (most advanced limitations). For analysis purposes, these WHO FC class values are transformed to a scale with scores ranging from 1–4; where a score of 1 corresponds to WHO FC Class I and a score of 4 corresponds to WHO FC Class IV. The higher scores indicate greater symptom severity or worse impact.

4.4.5.1. WHO FC III or IV (yes/no)

4.4.5.1.1. Definition of Endpoint

The exploratory endpoint of WHO FC III or IV (yes/no) is defined as the WHO FC categorization of III or IV (yes/no) at Day 1, and Weeks 4, 8, 12, 16 and 24 up to DBED + 7 days/OL Day 1 (the WHO FC value will be categorized as I/II or III/IV at every timepoint).

4.4.5.1.2. Analysis Methods

The proportion of participants, by intervention group overall, for the FAS, with WHO FC equal to III or IV will be described for every timepoint of assessment based on the number of participants

with available data (ie, those having a reported value of I through IV) and only considering values collected up to DBED + 7 days/OL Day 1. The proportion will be calculated at each timepoint of assessment and compared between the two intervention groups by means of a logistic regression model. The model will include randomized intervention, and the randomization stratification factors as fixed effects. The OR (selexipag/placebo) will be displayed with 2-sided 95% CIs.

A plot of the proportion of participants with WHO FC III/IV profile over time, by intervention group overall, for the FAS, will also be provided.

A listing of WHO FC over time will be provided on the FAS.

All recorded scheduled (and unscheduled) assessments will be assigned to the most appropriate analysis visit according to the best fitting analysis visit window for that assessment (see Section 4.1.1).

4.4.5.2. Change in WHO FC

4.4.5.2.1. Definition of Endpoint

The exploratory endpoint of change in WHO FC is defined as the change in WHO FC categorization from baseline to Weeks 4, 8, 12, 16, and 24 up to DBED + 7 days/OL Day 1.

All assessments (including unscheduled) are considered and reassigned to the most appropriate analysis visit according to the best fitting analysis visit window (see Section 4.1.1).

Changes from baseline in WHO FC values (I=1, II=2, III=3, IV=4) are categorized as improved (< baseline value), worsened (> baseline value) or unchanged (= baseline value) at every post-baseline assessment according to the following rules:

- An improvement corresponds to a decrease in WHO FC by at least one level whereas a worsening corresponds to an increase in WHO FC by at least one level.
- Participants remaining in the same WHO class as the one reported at baseline are categorized as unchanged.

4.4.5.2.2. Analysis Methods

Changes from baseline at each time point of assessment will be calculated at each post-baseline assessment based on the number of participants with non-missing data (ie, those having a reported value of I through IV) and will be displayed using shift tables by intervention group, overall, on the FAS. Change from baseline to worst post-baseline value will also be presented.

4.4.6. Change in Exercise Capacity

4.4.6.1. Definition of Endpoint

The exploratory endpoint of change in exercise capacity is defined as the change in exercise capacity from baseline to each time point of assessment up to DBED + 7 days as measured by the

6MWD in children ≥6 years of age who are developmentally able to understand and perform the test.

The variable of interest is 6MWD (m) expressed as change from baseline to each time point of assessment only considering values collected up to DBED + 7 days.

4.4.6.2. Analysis Methods

The change in 6MWD will be described by means of MMRM. The model will include randomized intervention, visit, intervention by visit interaction, the randomization stratification factors and baseline value as fixed effects. The variance-covariance matrix will be assumed to be unstructured. If convergence issues arise, a Toeplitz covariance structure will be considered. Other covariance structures will be considered after this if convergence issues remain. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Adjusted least squares (LS) means within each intervention group and intervention group comparison at each visit (estimated by the differences between LS means from the intervention by visit interaction) will be displayed along with their corresponding 2-sided 95% CIs, by intervention group, overall, on the FAS. Descriptive statistics of absolute values and change from baseline in 6WMD will also be included.

4.4.6.2.1. Subgroup Analysis

Treatment effect estimates and the corresponding 2-sided 95% CI will be presented as a forest plot for the FAS for the different levels of the following selected subgroups (see Table 11):

- WHO FC at randomization
- Number of PAH-specific therapies at randomization
- Region
- PAH etiology at randomization
- Age Cohort at randomization

A listing of 6MWD test results over time will also be provided on the FAS.

4.4.7. Change in Physical Activity (Actigraphy Measurements)

4.4.7.1. Definition of Endpoint

The exploratory endpoint of change in physical activity is defined as the change in physical activity (measured by an accelerometer/actigraph) from baseline to each scheduled visit (Week 12, Week 24, and Week 48) after randomization.

The accelerometry variables of interest include:

- Number of hours of daytime activity,
- Mean count per minute of daytime activity,
- Mean daily time spent in light physical activity,

- Mean daily time spent in moderate-to-vigorous physical activity as compared to time spent in sedentary, light, moderate, vigorous physical activity.

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 data are not collected before the respective study visits, the participant will collect the data during the 10 to 14 days following the visit. To be considered evaluable, physical activity should have been measured for at least 4 complete days at a specific timepoint of assessment. A complete day is defined as a record of at least 7 hours of daily awake daytime data, ie, a complete day if "WearAwakeMinutes" >=7*60 (after excluding the periods when the device was apparently not worn or worn during sleeping hours). These limitations allow for obtaining reliable results (Robertson 2011).

Baseline will be the average of up to 14 days prior to DBSD (average of at least 4 and up to 14 complete days between Day -41 and Day -1).

The post baseline value for a visit will be computed as the average of up to 29 days (average of at least 4 and up to 29 complete days) before or after the actual visit date ie, 14 days prior and 14 days after the actual visit day.

4.4.7.2. Analysis Methods

Changes from baseline at each time point of assessment will be calculated at each post-baseline assessment and will be displayed using summary tables by intervention group, overall, on the FAS.

Physical Activity/Actigraphy Parameters over time will also be listed, on the FAS.

4.4.8. Panama FC

The Panama Functional Classification contains 5 levels of functioning: Class I (No limitations), Class II (slight limitations), Class IIIa (marked limitations), Class IIIb (features of Class IIIa plus further marked limitations), and Class IV (most advanced limitations). For analysis purposes, these Panama FC values are transformed to a scale with scores ranging from 1–5; (I=1, II=2, IIIa=3, IIb=4, IV=5). The higher scores indicate greater symptom severity or worse impact.

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.

4.4.8.1. Panama FC IIIa/IIIb/IV (yes/no)

4.4.8.1.1. Definition of Endpoint

The exploratory endpoint of Panama FC IIIa/IIIb/IV (yes/no) is defined as the Panama FC IIIa/IIIb/IV (yes/no) at baseline and each scheduled visit up to DBED + 7 days/OL Day 1. Panama FC value is categorized as I/II or IIIa/IIIb/IV at every timepoint. The proportion of participants with Panama FC equal to IIIa/IIIb/IV is described for every timepoint of assessment based on the

number of participants with available data (ie, those having a reported value of I through IV) and only considering values collected up to DBED + 7 days.

All assessments (including unscheduled) are considered and re-assigned to the most appropriate analysis visit according to the best fitting analysis visit window (see Section 4.1.1).

4.4.8.1.2. Analysis Methods

Descriptive statistics (n, %) will be presented for the proportion of participants with Panama FC IIIa/IIIb/IV (yes/no) at each timepoint of assessment by intervention group, overall, on the FAS. The proportion will be calculated at each timepoint of assessment and compared between the two intervention groups by means of a logistic regression model. The model will include randomized intervention, and the randomization stratification factors as fixed effects. The odds ratio (selexipag/placebo) will be displayed with 2-sided 95% CIs.

A listing of Panama FC over time will also be provided on the FAS.

4.4.8.2. Change in Panama FC

4.4.8.2.1. Definition of Endpoint

The exploratory endpoint of change in Panama FC is defined as the change in Panama FC from baseline to each scheduled visit up to DBED + 7 days/OL Day 1.

All assessments (including unscheduled) are considered and re-assigned to the most appropriate analysis visit according to the best fitting analysis visit window (see Section 4.1.1).

Changes from baseline in Panama FC values (I=1, II=2, IIIa=3, IIb=4, IV=5) are categorized as improved (< baseline value), worsened (> baseline value) or unchanged (= baseline value) at every post-baseline assessment according to the following rules:

- An improvement corresponds to a decrease in Panama FC by at least one level whereas a worsening corresponds to an increase in Panama FC by at least one level.
- Participants remaining in the same Panama FC as the one reported at baseline are categorized as unchanged.

4.4.8.2.2. Analysis Methods

Changes from baseline at each time point of assessment will be calculated at each post-baseline assessment based on the number of participants with non-missing data (ie, those having a reported value of I through IV) and will be displayed using shift tables by intervention group, overall, on the FAS.

4.4.9. Ratio to Baseline in Serum NT-proBNP at each Timepoint of Assessment

4.4.9.1. Definition of Endpoint

The exploratory endpoint of ratio to baseline in serum NT-proBNP at each timepoint of assessment is defined as the ratio to baseline in serum NT-proBNP (ng/L) at each scheduled visit up to DBED + 7 days.

The ratio to baseline NT-proBNP at each scheduled visit is calculated as the ratio of the visit NT-proBNP value over the baseline value ie,

Ratio to baseline NT-proBNP = ([NT-proBNP at timepoint] / [NT-proBNP at baseline])

All assessments (including unscheduled) are considered and reassigned to the most appropriate analysis visit according to the best fitting analysis visit window (see Section 4.1.1). Ratio to baseline NT-proBNP will be calculated for observed values only (missing values will not be imputed).

4.4.9.2. Analysis Methods

Descriptive statistics for absolute values, absolute change from baseline values and ratio to baseline values for NT-proBNP including the geometric mean and 95% CI for ratio to baseline by each scheduled visit up to DBED + 7 days will be provided by intervention group on the FAS.

A plot of geometric mean and 95% CI for the ratio to baseline of NT-proBNP values over time will be provided for each intervention group and timepoint of assessment.

A listing of all observed NT-proBNP values, change from baseline and ratio to baseline over time will also be provided on the FAS.

4.4.10. Change in Echocardiography Variables

4.4.10.1. Definition of Endpoint

The following are exploratory echocardiographic variables:

Change from baseline to each scheduled visit of:

- Right ventricular systolic pressure (RVSP): a reduction from baseline is considered an improvement.
- Tricuspid annular plane systolic excursion (TAPSE): an increase from baseline is considered an improvement.
- Pulmonary artery acceleration time: an increase from baseline is considered an improvement.
- Left ventricular eccentricity index (LVEI, Diastole and Systole): a change towards 1 is considered an improvement.
- Right atrial area index (RAI): a decrease from baseline is considered an improvement.
- Tricuspid annular diameter: a decrease from baseline is considered an improvement.

4.4.10.2. Analysis Methods

The change in each echocardiographic variable, analyzed centrally, will be summarized by intervention group, overall, on the FAS. For each variable, the change from baseline to each scheduled timepoint up to DBED + 7 days will be summarized. Descriptive statistics for continuous variables will be displayed and the 2-sided 95% CIs of the mean will also be provided.

A listing of all observed echocardiographic variable values and change from baseline values over time will also be provided on the FAS.

4.4.11. Quality of Life (QoL)

4.4.11.1. Definition of Endpoint

Quality of Life will be assessed on the FAS in a subset of participating countries.

The following Pediatric Quality of Life Inventory™ (PedsQL™) questionnaires are used:

- PedsQL™ 4.0 SF15 Short Form Generic Core Scales score will assess the general physical, emotional, social and school functioning (15 questions)
- "Heart problems and treatment" component of PedsQL™ 3.0 Cardiac Module score (English-speaking US participants) (7 questions)
- "General fatigue" component of PedsQL™ Multidimensional Fatigue Scale score (English-speaking US participants) (6 questions)

The questionnaires are adapted for different age groups:

- For toddlers (2 to 4 years of age), a parent or caregiver completes the QoL questionnaire and rates each item using a 5-point Likert scale per item.
- For young children (5 to 7 years of age) a site study person reads the questions to the participant and asks the child to point to a 3-scale smiley score (Young Child Report). This score is then marked by the site study person.
- In the two older age groups (children of 8 to 12 and adolescents of 13 to 18 years of age) participants complete their age-adapted QoL questionnaire using a 5-point Likert scale per item.

A parent/caregiver additionally completes the QoL questionnaire (Parent Report) adapted to rate their young child, child, or adolescent also using a 5-point Likert scale per item.

For 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.

For participants growing into adults (reaching legal age) Parent Reports will not be collected.

Participants and parent(s)/caregiver(s) are asked to rate the QoL considering the 1-month period preceding the completion of the questionnaire.

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

4.4.11.2. Analysis Methods

The summary scores for each scale and dimension are calculated according to the algorithm in the scoring manual (Peds QL™ 2014). The total score is used for the analysis.

For 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.

QoL variables will be analyzed for participants and caregiver reports separately.

Descriptive statistics of absolute scores and change from baseline in QoL scores will be presented for each scheduled visit. Changes from baseline in QoL scores will be analyzed over time by means of a MMRM on values at Weeks 12, 24, and 48 up to DBED + 7 days in the QoL scores. The model will include randomized intervention, visit, intervention by visit interaction, the randomization stratification factor, and baseline value as fixed effects. Adjusted LS means within each intervention group and intervention group comparison at each visit (estimated by the differences between LS means from the intervention by visit interaction) will be displayed for each visit along with their corresponding 2-sided 95% CIs.

Listings for all QoL variables will also be provided.

4.4.12. Palatability of Study Intervention

4.4.12.1. Definition of Endpoint

The exploratory endpoint of palatability of study intervention is defined as the palatability of study intervention at Weeks 4 and 12 and at DBED and is determined by the response to 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 legally authorized representative (LAR(s)) or study site personnel.

4.4.12.2. Analysis Methods

Answers for each question in palatability will be summarized with counts and percentages by intervention group, overall, for each scheduled timepoint.

Palatability will also be listed.

4.4.13. Acceptability of Study Intervention

4.4.13.1. Definition of Endpoint

The exploratory endpoint of acceptability of study intervention is defined as the acceptability of the study intervention at Weeks 4 and 12, and at DBED, assessed using a 3-point categorical scale to determine whether the child swallowed the study intervention at the visits indicated in the assessment schedule.

The acceptability scale will be completed on a mobile electronic device (site tablet).

Parent(s) or LAR(s) or study site personnel will be asked, following the study intervention intake, whether the child swallowed the medication:

(a) fully,

(b) partially,

(c) not at all.

4.4.13.2. Analysis Methods

Answers for each question in acceptability will be summarized with counts and percentages by intervention group, overall, for each scheduled timepoint.

Acceptability will also be listed.

4.4.14. Right Ventricular Failure 5-criteria Severity Score (RVf-severity score)

4.4.14.1. Definition of Endpoint

The RVf-severity score is generated to reflect the extent of the right heart failure in children at baseline. This score was developed by the sponsor based on criteria that have been reported to reflect right heart function and disease prognosis (Hasan 2022; Tello 2018).

The RVf-severity score consists of the following 5 criteria:

1. Presence of severe heart failure symptoms (shortness of breath and/or cyanosis at rest).
2. Presence of clinical signs of congestion (hepatomegaly, peripheral edema and/or ascites).
3. Evidence of significant heart failure on echocardiogram as indicated by TAPSE <1.5 cm, TAPSE/sPAP ratio <0.19 mm/mmHg or right heart dilatation: right atrial area index >17 cm^2/m^2.
4. NT-proBNP levels above 300 ng/L.
5. Evidence of poor growth (the child's body weight lies below the 25^{th} percentile of CDC reference).

Each criterion is assigned a score of 1 if at least one element in the criterion is fulfilled, or 0 if no element within the criterion is fulfilled. The overall severity score is calculated by adding the scores for all assessed criteria and dividing by the number of criteria that can be assessed. The

overall severity score can have values between 0 and 1, where 0 indicates the least severe and 1 indicates the most severe right ventricular heart failure.

4.4.14.2. Analysis Methods

RVf-severity score at baseline is evaluated by treatment, by disease progression outcome, and by both factors combined. RVf-severity score will also be listed.

4.5. Safety Analysis

All safety analyses will be performed on the SAS, based on actual study intervention received, unless otherwise specified.

Analyses will include all data collected up to DBED + 30 days/OL Day 1, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N (number of non-missing observations), mean, SD, median, and range [minimum, maximum]. Categorical variables will be summarized using frequency counts and percentages.

All participant listings will be based on the SAS and sorted by intervention group, age cohort, site number, and participant number, unless otherwise specified.

4.5.1. Extent of Exposure

The extent of study intervention (selexipag or placebo) exposure during the DB period, measured in weeks, is considered in terms of DB study intervention duration (regardless of intervention interruptions). It is defined as the time interval (in weeks) between DBSD and the DBED inclusive, and calculated as:

$$(\text{DBED} - \text{DBSD} + 1) / 7.$$

Participant-years of study intervention will also be derived as extent of study intervention exposure (in days) for all participants / 365.25.

The number of participants who received study intervention will be summarized by intervention group, overall, by age cohort, and by body weight group categories at randomization (≥9 to <25 kg, ≥25 to <50 kg, ≥50 kg). Summaries will include descriptive statistics for total DB study intervention duration (in weeks; N, mean, SD, median, and range [minimum, maximum]) and participant-years of study intervention. In addition, total DB study intervention duration will be summarized with the number and percentage of participants in the following duration categories (where applicable): <4 weeks, 4 - <8 weeks, 8 - <12 weeks, 12 - <16 weeks, 16 - <24 weeks, 24 - <36 weeks, 36 - <48 weeks, 48 - <60 weeks, and ≥60 weeks, as well as the cumulative distribution of duration by class interval (ie, at least 4, 8, 12, 16, 24, and 36 weeks, and every 12 additional weeks thereafter).

The individual maximum tolerated dose (iMTD) is defined for each participant (within the study intervention dose range according to body weight group categories) as the intervention dose reached at the end of the uptitration period.

The iMTD is defined as the dose received on the first day following the Week 12 visit. For participants who prematurely discontinue the study intervention earlier, it is defined as the highest daily dose (twice daily; bid) where the reason for stopping this dose level is not "dose reduction" or "discontinuation"; if no up-titration attempt has been made, then iMTD is defined as zero.

The iMTD for the DB treatment period will be summarized with descriptive statistics (N, Mean SD and range), and the number and percentage of participants in each iMTD dose level will also be presented.

Further, summary tables will be presented, overall and by age cohort, for the incidence and reason for study intervention dose adjustment (dose reduced or dose interrupted), including whether any dose adjustment was COVID-19 related. Summaries will also include the number and percentage of participants who permanently discontinued study intervention.

Study intervention administration (data recorded in the 'Study Drug Administration for Selexipag or Placebo – Double Blind Treatment' eCRF form) will also be listed, including the reason for dose adjustment and whether or not the dose adjustment was COVID-19 related (if applicable). In this listing the iMTD reached for each participant will also be indicated.

As participants may initiate bosentan rescue treatment during the study (following a PAH disease progression), bosentan administration (all records in the 'Study Drug Administration for Bosentan - Double Blind Treatment' eCRF form) will be listed, based on the subset of participants who initiate bosentan (with a non-missing bosentan rescue treatment start date, as defined in Section 4.1.7).

4.5.2. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the latest implemented Medical Dictionary for Regulatory Activities (MedDRA) version.

For the analysis of AEs, the 30-day time window after DBED is split into two intervals: one including AEs up to 3 days after DBED or OL Day 1 for those participants entering the OLEP, and a second one including AEs with onset from day 4 to day 30 after DBED for participants not entering OL. The 3 days window corresponds to 5 pharmacological half-lives of selexipag's active metabolite, which defines AEs to be treatment-emergent.

Imputation rules for missing or incomplete start or end date of AEs are described in Section 4.1.12.

For each AE, the number and percentage of participants who experience at least one occurrence of the given event will be summarized by intervention group, by system organ class (SOC) and preferred term (PT) in descending order of frequency in the selexipag intervention group. If

frequency counts of individual SOC and/or PTs are the same, then alphabetical order will be used. Verbatim terms will be included only in listings.

Adverse event definitions

Treatment-emergent AEs (TEAEs) during the DB treatment period

Any AE occurring on or after the initial administration of study intervention through the day of last dose in the DB treatment period plus 3 days (DBED + 3 days) and/or prior to start of OL study administration (as participants transition without interruption to the OLEP) is considered to be treatment-emergent. For participants who transition to the OLEP and have their first OL dose (evening dose) on the same day (OL Day 1) as their EDBT dose (morning dose), then their event(s) occurring on OL Day 1 are assigned to the DB treatment period (time of dosing and events are not recorded). If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment-emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment-emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported TEAEs will be included in the analysis. As described in Section 4.1.11, the naming convention for safety endpoints of interest to be adopted for TEAEs in the DB treatment period is up to DBED + 3 days/OL Day 1.

Serious AEs (SAEs)

An AE is considered serious if the tick box 'Yes' for 'Serious?' is checked on the AE eCRF page.

Treatment-emergent SAEs (TESAEs)

Treatment-emergent SAEs are defined in the same way as for TEAEs / SAEs.

Post-treatment AEs (PTAEs)

Any AE which is not considered a TEAE ie, with onset on or after (DBED + 4 days) and up to 30 days after DBED, is considered to be a PTAE (only applicable for participants not entering OL).

Post-treatment SAEs (PTSAEs)

Post-treatment SAEs are defined similarly to PTAEs / SAEs.

Observation Period AEs (OPAEs)

For the subset of participants who prematurely discontinue DB study intervention and did not discontinue from the study, Observation Period AEs are defined. They are all AEs with onset after DBED (see Section 4.1.5) + 30 days and up to the end of the DB period.

Observation Period SAEs (OPSAEs)

Observation Period SAEs are similarly defined as OPAEs / SAEs.

Adverse events leading to discontinuation of study intervention

An AE is considered as leading to discontinuation of study intervention if the tick box 'Drug withdrawn' of the 'Action taken with Selexipag or Placebo' is checked on the "Adverse Event" eCRF page.

Adverse events leading to discontinuation of bosentan rescue treatment

An AE is considered as leading to discontinuation of bosentan rescue treatment administration if the tick box 'Drug withdrawn' of the 'Action taken with Bosentan' is checked on the "Adverse Event" eCRF page.

Bosentan-emergent AEs (BEAEs)

Any AE occurring on or after bosentan rescue treatment start date (see Section 4.1.7.1) and up to the bosentan rescue treatment end date (see Section 4.1.7.2) + 7 days is considered to be bosentan-emergent (BE). The 7 days window corresponds to 5 pharmacological half-lives of bosentan.

All reported BEAEs will be included in a listing.

COVID-19 related AEs, SAEs, and non-serious AEs

An AE is considered COVID-19 related event based on the COVID-19 Standardized MedDRA Query (SMQs)/PTs in the current MedDRA version.

- **Adverse event summaries**
- Summary tables will be provided for TEAEs (overall and by age cohort):
- AEs
- SAEs
- AEs leading to discontinuation of study intervention
- AEs by severity
- Severe AEs
- AEs by relationship to study intervention
- AEs related to study intervention
- AEs leading to dose reduction or interruption of study intervention
- SAEs with fatal outcome
- Overall summary table including the number and percentage of participants with one or more:
  - AEs (with subcategories of AEs related to study intervention and related non-serious AEs)
  - AEs with fatal outcome (with subcategory of AEs related to study intervention)
  - SAEs (with subcategory of SAEs related to study intervention)

- AEs leading to discontinuation of study intervention (with subcategory of AEs related to study intervention)
- AEs by severity
- COVID-19 associated AEs (with subcategories of serious and non-serious AEs).

Summary tables will also be provided for TEAEs and TESAEs by body weight group categories at randomization (≥9 to <25 kg, ≥25 to <50 kg, ≥50 kg).

For TEAEs and TESAEs, exposure-adjusted incidence rates will also be summarized by intervention group, by SOC and PT within each SOC, overall and by age cohort.

The exposure-adjusted incidence rate for an event is defined as the number of participants exposed to the study intervention and experiencing a certain event divided by the total exposure time of all participants who are at risk for the event. Specifically, for participants with no event, the exposure time is the time from the DBSD to the DBED + 3 days/OL Day 1; for participants with at least one event, the exposure time is the time from the DBSD to the onset of the first event.

Summary tables will also be provided for all AEs and SAEs up to DBED + 3 days/OL Day 1 (overall and by age cohort, and by body weight group category) by PT only.

Most frequent TEAEs (at least 5% of participants who experience at least one occurrence of the given event in any arm) will also be summarized by PT.

Summary tables will also be provided for all AEs and SAEs up to DBED + 30 days (overall and by age cohort).

Treatment-emergent COVID-19 associated AEs will also be summarized, by intervention group, overall, by SOC and PT.

In addition to the summary tables, listings will be provided for participants who:

- Had AEs
- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had SAEs with fatal outcome.

The type of AE (ie, TEAE, PTAE, or OPAE) will be specified in the listings.

Listings will also be provided for participants who:

- Had SAEs during the screening period (SAEs with onset before DB study intervention start)
- Had AEs for participants on bosentan rescue treatment
- Had AEs leading to discontinuation of bosentan rescue treatment.

COVID-19 associated AEs during study will also be listed.

4.5.2.1. Adverse Events of Special Interest (AESI)

Incidence of other treatment-emergent AESI will be summarized. See Section 6.7 Appendix 7 for list of AEs in each category.

Incidence of treatment-emergent AESI (defined similarly to the TEAEs) will be summarized by intervention group, by each individual AESI category and PT (in descending order of frequency in AESI category, in the selexipag intervention group). An overall table summary will be provided, as well as by age cohort, and by weight category (≥9 to <25 kg, ≥25 to <50 kg, ≥50 kg).

In addition, the summary tables will include:

- Number and % of participants with at least one AESI
- Relative risk with 95% CI for selexipag vs. placebo
- Number and % of participants with at least one AESI leading to permanent discontinuation of study intervention (PTs for AESI leading to discontinuation will also be provided)
- Number and % of participants with at least one serious AESI (PTs for serious AESIs will also be provided)
- Number and % of participants with at least one related AESI
- Number and % of participants with at least one fatal AESI
- Number and % of participants with at least one event within the worst severity category where the following hierarchical order is considered to determine worst severity: Severe, Moderate, Mild, Missing
- For recurrent events:
  - Cumulative number of recurrent AESIs (note: this includes the total number of events as participants may have multiple PTs under an AESI category, and multiple events in a given PT)
  - Average annualized event rate (AER)

    where AER (per PY) $= \left(\frac{Cumulative\ number\ of\ recurrent\ events}{PY\ \ intervention\ exposure}\right)$
  - Participant Years (PY) of intervention exposure (calculated as indicated in Section 4.5.1) and is further based on first dose of study intervention up to DBED + 3 days/OL Day 1
  - Outcome for cumulative number of recurrent AESIs
    - Number and % of fatal events
    - Number and % of not recovered/not resolved events
    - Number and % of events that recovered/resolved with sequelae
    - Number and % of recovered/resolved events
    - Number and % of events with unknown outcome

A listing of treatment-emergent AESIs will also be provided.

AESIs categories have been defined based on important identified or potential risks described in the selexipag Core RMP summary of safety concerns. In addition, other events of interest include Prostacyclin-associated reactions, Pregnancy, and COVID-19 infection. Summary tables for these topics will be similar to those above; further details are provided below for the individual events.

Prostacyclin-associated reactions

An overall table of summary of treatment-emergent prostacyclin-associated reactions will be provided, as well as by age cohort.

Treatment-emergent prostacyclin-associated reactions will also be reported by PAH-specific therapy at baseline (ERA monotherapy, PDE-5 inhibitor monotherapy (or sGCs monotherapy), combination of both ERAs and PDE-5 inhibitors (or sGCs); see Section 6.8 Appendix 8).

In addition, treatment-emergent prostacyclin-associated reactions will be summarized separately for participants:

- reaching the maintenance period (ie, who do not prematurely discontinue study intervention during the uptitration period and so perform the Week 12 visit):
  - prostacyclin-associated reactions in the uptitration (those with onset on or after study intervention start and up to the day before the Week 12 visit day) and maintenance (those with and onset on or after the Week 12 visit and up to DBED + 3 days) periods will be summarized separately. Participants who prematurely discontinued study intervention before the Week 12 visit are excluded from this analysis and therefore from the denominator.
- whether reaching the maintenance period or not
  - prostacyclin-associated reactions in the uptitration period (those with onset on or after study intervention start and up to the day before the Week 12 visit day or, for participants who discontinued study intervention before the Week 12 visit, up to DBED + 3 days) will be summarized.

This summary will also display the participant-years of intervention in the uptitration and maintenance periods.

The extent of study intervention exposure in the uptitration period will be calculated as follows:

- If the participant does NOT prematurely stop study intervention before the Week 12 visit, the extent of exposure (days) = Week 12 visit day – [DBSD].
- If the participant prematurely stops study intervention before the Week 12 visit, the extent of exposure (days) = DBED – [DBSD] + 1.

The extent of study intervention exposure in the maintenance period will be calculated as follows:

- If the participant does NOT prematurely stop study intervention before the Week 12 visit, the extent of exposure (days) = [DBED] – [Week 12 visit day] + 1.
- If the participant prematurely stops study intervention before the Week 12 visit, the extent of exposure will not be calculated, and the participant will be excluded from the denominator.

A listing of treatment-emergent prostacyclin-associated reactions will also be provided.

Pregnancy

Treatment-emergent AESI for pregnancy will be summarized by intervention group, overall.

COVID-19 Infection

Treatment-emergent AESI for COVID-19 infection will be summarized by intervention group, overall.

4.5.2.2. Deaths

The date of death (from any cause) and its primary cause are recorded in the eCRF "Death Information" form.

Deaths will be displayed by actual intervention received. Summary tables will be provided for (overall and by age cohort):

- All deaths
- Deaths that occurred up to DBED + 3 days
- Deaths that occurred up to DBED + 30 days

Frequencies for the following parameters will be included in the summary tables:

- Number of participants who died
- Primary cause of death
- Related to study intervention
- COVID-19 associated

A listing of participants who died during the study will also be provided. Deaths that occurred up to DBED + 3 days, and deaths that occurred up to DBED + 30 days will be flagged.

4.5.3. Additional Safety Assessments

4.5.3.1. Clinical Laboratory Tests

All central laboratory data will be considered regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments. All recorded assessments will be assigned to the most appropriate analysis visit according to the best fitting analysis visit window for that assessment (see Section 4.1.1). Both central and local laboratory data will be used to evaluate abnormalities.

List of laboratory parameters

Clinical Chemistry	Hematology
Alanine aminotransferase (ALT) (Enzyme U/L)	Hematocrit (L/L)
Albumin (g/L)	Hemoglobin (g/L)
Alkaline phosphatase (Enzyme U/L)	Platelet count (10^9/L)

Aspartate aminotransferase (AST) (Enzyme U/L)	Erythrocytes (10^12/L)
Bicarbonate (mmol/L)	Leukocytes (10^9/L) with Differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) Fraction of 1 for Differential/Leukocytes (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
Bilirubin (µmol/L)	Erythrocyte mean corpuscular volume (fL)
Blood urea nitrogen (BUN) (mmol/L)	
Calcium (mmol/L)	
Cholesterol (mmol/L)	
Chloride (mmol/L)	
Creatinine (µmol/L)	
Creatinine clearance (mL/s)	
Direct bilirubin (µmol/L)	
Free T3 and free T4 (pmol/L) (assessed in case Thyrotropin/TSH is abnormal or when medically indicated)	
Gamma glutamyl transferase (Enzyme U/L)	
GFR from serum creatinine adjusted for BSA (mL/s/m2)	
Glucose (mmol/L) (no fasting requirements)	
Potassium (mmol/L)	
Sodium (mmol/L)	
Thyroid antibodies (Antithyroglobulin & Thyroperoxidase antibody) (U/mL) (assessed at Visit 2 and thereafter only when medically indicated)	
Thyrotropin/TSH (mIU/L)	
Urate (µmol/L)	

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled timepoints (Baseline, Week 4, 8, 12, 16, and 24 and every 12 weeks thereafter) by intervention group, overall and by age cohort. An overall summary timepoint will also be included, which is the description of all post-baseline analysis visit measurements over time (up to DBED + 3 days) across all participants. Change from baseline to each scheduled post-baseline assessment will also be summarized. Thyroid antibodies and Free T3/Free T4 will be excluded from the summary table(s) since these are not assessed at regular timepoints; only when medically indicated or in the case where Thyrotropin/TSH is abnormal. For participants with abnormal (present) thyroid antibodies at baseline, Thyrotropin/TSH will be listed.

For descriptive statistics presentations only, to account for changing reference ranges across age and sex, certain central and local laboratory parameter values (Y_{ori}) and their reference ranges (LLN_{ori}, ULN_{ori}) will be normalized as Y_{norm} using a standard range (LLN, ULN) as follows:

$$Y_{norm} = LLN + \frac{(Y_{ori} - LLN_{ori})}{(ULN_{ori} - LLN_{ori})} X\ (ULN - LLN)$$

The laboratory tests that require normalization and their standard ranges to be used are:

Laboratory Parameter	**Standard Range**	
	LLN	**ULN**
Clinical Chemistry:		

Laboratory Parameter	Standard Range	
	LLN	ULN
Alanine aminotransferase (ALT) (Enzyme U/L)	6	34
Albumin (g/L)	33	47
Alkaline phosphatase (Enzyme U/L)	31	110
Aspartate aminotransferase (AST) (Enzyme U/L)	10	40
Bicarbonate (mmol/L)	19.3	29.3
Cholesterol (mmol/L)	3.23	5.48
Creatinine (µmol/L)	40	83
Gamma glutamyl transferase (Enzyme U/L)	4	49
Thyrotropin /TSH (mIU/L)	0.34	5.60
Urate (µmol/L)	137	404
Hematology:		
Hematocrit (L/L)	0.34	0.48
Hemoglobin (g/L)	116	164
Platelet count (10^9/L)	140	400
Erythrocytes (10^12/L)	4.1	5.6
Leukocytes (10^9/L)	3.80	10.70
Neutrophils (10^9/L)	1.65	8.15
Lymphocytes (10^9/L)	0.95	5.25
Monocytes (10^9/L)	0.40	-0.90
Eosinophils (10^9/L)	0.00	0.20
Erythrocyte mean corpuscular volume (fL)	79	96

A summary of the overall shift (at any time) during the DB treatment period (DBED + 3 days) will be provided for the same chemistry and hematology parameters, by intervention group, overall and by age cohort, with respect to the following overall post-baseline assessment (at any time):

Baseline assessment	Post-baseline assessments:	Overall post-baseline assessment
Low	At least one Low (and no High)	Low
	At least one High	High
	All Normal	Normal
Normal	At least one Low	Low*
	At least one High	High*
	All Normal	Normal
High	At least one Low	Low
	At least one High (and no Low)	High
	All Normal	Normal

*Participants who have a Normal baseline assessment, and both Low and High post-baseline assessments will be counted in both categories.

Shift from baseline up to last post-baseline value during DB treatment period (DBED + 3 days) will also be included.

Marked Laboratory Abnormalities are defined in Section 6.9 Appendix 9.

Treatment-emergent marked laboratory abnormalities are defined as:

- Any abnormality with onset on or after DBSD (see Section 4.1.3) up to DBED + 3 days (see Section 4.1.5).
- If the abnormality occurs on the day of the initial administration of study intervention, and either the laboratory collection time or time of study intervention administration are missing,

then the abnormality will be assumed to be treatment-emergent. If the date of the abnormality is recorded as partially or completely missing, then the abnormality will be considered as treatment-emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date.

- If the abnormality was present at baseline, then any post-baseline abnormality will be considered as treatment-emergent only if the post-baseline abnormality is in a category worse than at baseline.
- In case the marked abnormality is defined as an increase from the baseline (eg, hemoglobin), comparison of the central laboratory baseline value with the local laboratory post-baseline value to assess the marked abnormality is allowed.

The number and percentage of participants with treatment-emergent marked abnormal values will be presented for each chemistry and hematology laboratory parameter for which marked abnormalities are defined (see Section 6.9 Appendix 9), by intervention group, overall and by age cohort. Percentages are calculated as the number of participants with at least one post-baseline value for the abnormality for the laboratory parameter under consideration divided by the number of participants with any post-baseline laboratory measurement (and for hemoglobin and creatinine, also with a valid baseline value based on the definition of the marked abnormalities, as provided in Section 6.9 Appendix 9).

In addition to the summary tables, chemistry and hematology laboratory data will be listed, including a "Marked Abnormality" column. Data coming from local laboratories will be flagged.

An evaluation of drug-induced serious hepatotoxicity (e-DISH) plot of the maximum treatment-emergent ALT or AST (in multiples of ULN) by maximum treatment-emergent bilirubin (in multiples of ULN) will be presented to detect potential cases of drug-induced liver toxicity. Reference lines of ≥3 x ULN for ALT/AST and ≥2 x ULN for bilirubin will be drawn and number and percentage of participants in each quadrant will be displayed.

Separate tables and listings of liver function test (LFT) abnormalities will be provided. The listing of LFT abnormalities will also include the ALT/AST and bilirubin values in multiples of ULN corresponding to the e-DISH plot.

Red blood cell morphology will be listed with all central laboratory variables.

Serum and urine pregnancy test results from central laboratory data and from the eCRF dedicated form will also be listed for females of childbearing potential that are sexually active.

4.5.3.2. Vital Signs and Physical Examination Findings

4.5.3.2.1. Vital Signs and Growth

Vital Signs

Continuous vital sign parameters include pulse and blood pressure (systolic and diastolic).

Continuous vital sign parameters will be summarized by intervention group, overall and by age cohort, at each assessment time point (Week 4, 8, 12, 16, and 24 and every 12 weeks thereafter) with descriptive statistics. An overall summary timepoint will also be included, which is the description of all post-baseline analysis visit measurements over time (up to DBED + 3 days) across all participants. Change from baseline to each post-baseline scheduled visit will also be summarized. In addition, changes in blood pressure (systolic and diastolic), and pulse will be analyzed DBED + 3 days by means of an MMRM on values at each scheduled visit. The model will include intervention received, visit, intervention by visit interaction, the IWRS stratification factors and the baseline value as fixed effects. The variance-covariance matrix will be assumed to be unstructured. If convergence issues arise, a Toeplitz covariance structure will be considered. Other covariance structures will be considered after this if convergence issues remain. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Growth

Growth variables are Body Mass Index (BMI) (kg/m^2), body weight (kg) and height (cm).

BMI will be calculated as weight (kg)/(height (m))^2, at each assessment time point (Week 12, 16, and 24 and every 12 weeks thereafter) when body weight is measured. The height measurement collected at the nearest visit will be used in the calculation. In the case of equally distant assessments, the earlier will be used.

Growth variables will be summarized by intervention group, overall and by age cohort, at each assessment time point in terms of absolute values and change from baseline to each post-baseline scheduled visit. An overall summary timepoint will also be included, which is the description of all post-baseline analysis visit measurements over time (up to DBED + 3 days) across all participants. In addition, changes from baseline will be analyzed by means of an MMRM as described for vital signs.

Body weight and height will also be assessed by intervention group, overall and by age cohort, using the shifts from baseline to last follow-up visit before DBED + 3 days in percentiles of CDC growth references. Similarly, BMI will be presented by intervention group, overall.

Body weight (kg) and height (cm) will be plotted over time as individual curves per participant. The x-axis will display age in years The y-axis will display the growth variable of interest, weight (kg) or height (cm). Separate figures will be created for male and female participants, with or without Down Syndrome, with overlays of sex-specific standard CDC growth references by age for the 5th, 25th, 50th, 75th, and 95th percentiles. All collected values of weight and height will be used. A different symbol will be used for each intervention group.

Growth variables and vital signs parameters will also be listed.

Separate listings of participants with weight and height, and BMI growth percentiles from baseline to last follow-up visit through DBED + 3 days will also be presented.

4.5.3.2.2. Physical Examination

Physical examination assessments are not collected in the eCRF. The date of the physical examination is collected in the eCRF and clinically relevant findings that are present prior to signing of informed consent form (ICF) should be recorded on the Medical History eCRF page (see protocol Section 8.3.1). Physical examination findings made after the ICF is signed, which meet the definition of an AE (see protocol Section 8.6), should be recorded on the AE page of the eCRF.

4.5.3.3. Electrocardiogram

A central ECG service is used for the ECG evaluation (see protocol Section 8.3.3).

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval, using the following correction methods: Bazett's formula (QTcB) and Fridericia's formula (QTcF).

Descriptive statistics of ECG parameters at baseline and change from baseline will be summarized by intervention group, overall and by age cohort, at each scheduled visit. An overall summary timepoint will also be included, which is the description of all post-baseline analysis visit measurements over time (up to DBED + 3 days) across all participants. Change from baseline will be analyzed by means of an MMRM as described for vital signs in Section 4.5.3.2.1.

For QTcB and QTcF, values and changes from baseline are categorized as in Table 9:

Table 9: Marked Abnormality Criteria for QTc Values and Changes from Baseline

QTc Abnormality criteria	QTc Abnormality criteria	Marked abnormality criteria flag
QTc (msec)	≤450	
	>450 – 480	H
	>480 – 500	HH
	>500	HHH
QTc change from baseline (msec)	≤30	
	>30 – ≤60	HH
	> 60	HHH
QTc value > 450 msec and QTc interval increase from baseline > 30 msec		

At each time point of assessment, the number and percentage of participants within these categories will be presented by intervention group, overall and by age cohort.

Qualitative ECG abnormalities after baseline are defined as all qualitative abnormalities with onset after DBSD (see Section 4.1.3) up to DBED + 3 days (see Section 4.1.5) that were not present at baseline and are reported by the central ECG reader. All qualitative ECG abnormalities collected and provided will be considered.

The number and percentage of participants who experienced treatment-emergent ECG abnormalities will be summarized by intervention group, overall and by age cohort.

In addition, qualitative ECG abnormalities at baseline will be similarly summarized.

All ECG data will be listed, and critical changes (> 30 msec) in QTcB and/or QTcF (as defined above) will be flagged.

4.6. Other Analyses

4.6.1. Sexual Maturation (Tanner Stage) and Childbearing Potential

The sexual maturation will be measured by the Tanner stage (see protocol Section 8.3.4).

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 stopped once full sexual maturation is reached (if applicable before EDBT).

In addition, for female participants, childbearing potential is assessed.

Childbearing potential at baseline and last available assessment through DBED + 3 days will be summarized by intervention group, overall and by age cohort, on the SAS. Shift from baseline to last available assessment through DBED + 3 days for any status changes during the study ("Of childbearing potential" and "Not of childbearing potential" ie, "Premenarchal" or "Not applicable"), will be presented.

Tanner stage at baseline and last available assessment through DBED + 3 days will be summarized by intervention group, overall and by age cohort, on the SAS. Change from baseline in categories at last available assessment through DBED + 3 days will also be presented using shift tables.

Listings for Tanner stage and childbearing potential will also be provided, on the SAS.

4.6.2. Pharmacokinetics/Pharmacodynamics

PK analyses are not covered in this SAP and will be described in a separate Clinical Pharmacology Analysis Plan.

4.6.3. Right Heart Catheterization

Right heart catheterization (RHC) is not a mandatory study specific assessment but might be performed during the study for any medical reason, as judged by the investigator, and results should be recorded in the eCRF (see protocol Section 8.2.8).

Table 10 presents a list of RHC variables.

Table 10: RHC Variables

Variable	Summary type
RHC (Yes/No)	Frequency distribution with the number and percentage of participants in each category.
Pulmonary Vascular Resistance index (PVRi) (Wood units x m^2)	Descriptive statistics (N, mean, SD, median and range [minimum and maximum]).
Mean pulmonary arterial pressure (mPAP) (mmHg)	
Pulmonary arterial wedge pressure (PAWP) (mmHg)*	
Left Ventricular End Diastolic Pressure (LVEDP) (mmHg)	
Left atrial pressure (LAP) (mmHg)	

Fick Cardiac Output (CO) method (L/min)	
Thermodilution Cardiac Output (CO) method (L/min)	
Time from RHC (days)	

RHC = right heart catheterization; SD = standard deviation.
*Left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) (mmHg). The number and percentage of the alternative measures will be also shown.

Time from RHC (days) is defined as the time from RHC to randomization.

RHC variables used to diagnose PAH at baseline will be summarized by intervention group, overall, on the FAS.

All RHC variables (for RHC performed prior to and during the study) will be reported in participant listings based on a subset of participants in the FAS who had a RHC performed.

4.6.4. Health Economics

All-cause hospitalizations are taken from the Adverse Events/Serious AEs eCRF page in which hospital admission dates are documented. PAH-related hospitalizations are defined as those ticked as "Was hospitalization due to PAH worsening?".

The analyses will be conducted on the FAS, overall.

The timeframe considered for these endpoints is from randomization to DBED + 7 days/OL Day 1, as defined in Section 4.1.11.

4.6.4.1. Annualized number of hospitalizations (for all causes)

The number of hospitalizations initiated after randomization up to the DBED + 7 days/OL Day 1 is annualized by multiplying with 365.25 days divided by (DBED + 7 days/OL Day 1 minus randomization date + 1).

Number of hospitalizations and corresponding exposure duration will be summarized by intervention group.

A negative binomial regression model with intervention group as the only covariate and exposure duration as offset will be used to obtain point estimate and 95% CI for mean annualized number of hospitalizations for each intervention group as well as point estimate and 95% CI for rate ratio of selexipag vs placebo. The two-sided Wald-type test p-value will be provided for descriptive purpose.

4.6.4.2. Annualized number of PAH-related hospitalizations

The number of PAH-related hospitalizations initiated after randomization up to the DBED + 7 days/OL Day 1 is annualized by multiplying with 365.25 days divided by (DBED + 7 days/OL Day 1 minus randomization date + 1).

Analysis will be performed as per Section 4.6.4.1.

4.6.4.3. Annualized number of days spent in hospital for all causes

For each hospitalization, the number of days in hospital is calculated as discharge date minus admission date + 1 ie, participants who are admitted and discharged on the same day will not be included.

For each participant, the number of days spent in hospital is the sum of the number of days in hospital for all his/her hospitalizations up to DBED + 7 days/OL Day 1. If DBED is missing or incomplete or OL Day 1 is incomplete, the imputation rules in Section 4.1.12 will be applied.

The number of days spent in hospital for all causes is annualized by multiplying with 365.25 days divided by (DBED + 7 days/OL Day 1 minus randomization date + 1).

Descriptive statistics for each intervention group will be provided. The (annualized) number of days spent in hospital is not expected to follow a specific type of distribution; therefore, the p-value from the non-parametric Wilcoxon-Mann-Whitney test will be provided for descriptive purpose only.

4.6.4.4. Annualized number of days spent in hospital for PAH-related causes

For each hospitalization for PAH-related causes, the number of days in hospital is calculated as discharge date minus admission date + 1 ie, participants who are admitted and discharged on the same day will not be included.

For each participant, the number of days spent in hospital for PAH-related causes is the sum of the number of days in hospital for all his/her hospitalizations for PAH-related causes up to DBED + 7 days/OL Day 1. If DBED is missing or incomplete or OL Day 1 is incomplete, the rules in Section 4.1.12 will be applied.

The number of days spent in hospital for PAH-related causes is annualized by multiplying with 365.25 days divided by (DBED + 7 days / OL Day 1 minus randomization date + 1).

Analysis will be performed as per Section 4.6.4.3.

4.6.5. Definition of Subgroups

To assess the consistency of the study intervention effect across different participant subgroups, analyses will be performed on the primary efficacy endpoint, and the secondary efficacy endpoint for NT-proBNP, classifying participants according to relevant demographic characteristics as defined in Table 11.

Subgroup analyses are descriptive/exploratory in nature and will not be adjusted for multiplicity. Participants with undetermined subgroups due to missingness will not be included in the subgroup analyses.

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

Table 11: Definition of Subgroups

Subgroup	Definition
WHO FC at randomization[a]	• **II** • III
Sex	• **Male** • Female
Number of PAH-specific therapies at randomization[a]	• **Monotherapy (1)** • Combination Therapy (≥2)
PAH etiology at randomization	• **Idiopathic PAH, Heritable PAH, PAH associated with HIV infection, Drug- and toxin-induced PAH, PAH with coincidental CHD** • CHD post-operative
Region	• **North America,** Western Europe • Eastern Europe • Asia • Latin America
Body weight category at randomization	• **≥9 to <25 kg,** • ≥25 to <50 kg • ≥50 kg
Age Cohort at randomization	• **Cohort 1 (≥ 12 - < 18 years)** • Cohort 2 (≥ 6 - < 12 years) • Cohort 3 (≥2 - < 6 years)
NT-proBNP at baseline	• <300 ng/L • ≥300 ng/L

[a]as per IWRS
CHD = Congenital heart disease; HIV = Human immunodeficiency virus; PAH = Pulmonary arterial hypertension; WHO FC = World Health Organization functional class.

4.7. Interim Analyses

There are no inferential interim analyses planned for any efficacy endpoint.

The database will be locked, and the data extracted and analyzed at 3 timepoints during the DB period of the study (see Section 1.2.1).

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Section 6.10 Appendix 10 contains details of the endpoints included at each of the analysis timepoints.

4.7.1. Data Monitoring Committee (DMC) or Other Review Board

4.7.1.1. Independent Data Monitoring Committee

The IDMC has the overall responsibility for safeguarding the interests of participants by monitoring safety data obtained during 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 was 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.

The IDMC is tasked with organizing and conducting data reviews with the assistance of an independent SSG. The IDMC will make appropriate recommendations based on summaries provided by the SSG team, based on an IDMC SAP for closed sessions, prepared in accordance with the IDMC Charter (see IDMC Charter Section 8 for details).

4.7.1.2. Other Review Boards

A CEC is appointed to review and adjudicate, in a blinded fashion, each suspected disease progression event. 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.

In addition, the primary reason for hospitalization and cause of death will be adjudicated. Any relevant supporting information (hospital discharge summaries, local laboratory, or imaging data, etc.) will be provided to the CEC. Full details on the procedure, as well as the composition and operation of the CEC, are described in the CEC charter.

4.8. Changes to Protocol-Planned Analyses

Some endpoints and analyses have been added or adapted compared to the protocol planned analyses. A summary is provided below:

Section 3 Analysis Sets:

- Removed PK Analysis Set (PKAS) - PK analyses are not covered in this SAP.
- Removed Quality of Life Analysis Set (QoLS) - QoL analyses are conducted on the FAS.

Section 4.1.14, Right Ventricular Failure 5-criteria Severity Score (RVf-severity score)

- RVf-severity score is not specified in the protocol. Definitions and analyses for this endpoint are described in Section 4.4.14.

Section 4.6.1, Sexual Maturation (Tanner Stage):

- Change from baseline in Tanner stage is presented to the last available assessment through DBED + 3 days, rather than to all assessed timepoints as stated in the protocol Section 3.

Section 4.5.3.2.1, Vital Signs and Growth

- Growth parameters: Because WHO weight references are not available beyond 10 years of age, CDC growth references were used in the actual analysis so that weight percentiles can be provided for all participants (age ≥2 to <18 years) in the study. For consistency, height and BMI percentiles were also derived based on CDC references. CDC growth references were also applied in Analysis 1 and Analysis 2.

Section 4.6.4, Health Economics:

- Health economic endpoints are not specified in the protocol. Definitions and analyses for health economic endpoints of interest are described in Section 4.6.4.

5. SAMPLE SIZE DETERMINATION

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Table 12: CCI

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Participant Dispositions

The number and percentage of participants in the following disposition categories will be summarized on the SCR throughout the study overall:

- Participants screened (number of (unique) participants entering screening in the IWRS system).
- Screening failures (participants with 'Screen Failure' ticked in the 'Trial Disposition (Completion/Discontinuation)' eCRF page). The primary reason for screening failure will be provided, including any COVID-19 related reasons (categorized as AE, death or other). In case re-screening resulted in study enrollment, the participant is not considered as a screening failure. In case re-screening resulted in a screening failure, only the reason for screening failure related to the re-screening is considered.
- Participants re-screened (participants with at least two screening dates).

The number and percentage of participants in the following disposition categories will be summarized on the FAS by intervention group, overall and by age cohort.

- Participants randomized (participants with a randomization number recorded in the 'Randomization' eCRF page).
- Participants who received DB study intervention (with at least one record collected in "Study Drug Administration for Selexipag or Placebo - Double Blind Treatment" eCRF page).
- Participants who prematurely discontinued the study during the DB period (all participants with 'Discontinued' ticked as Subject's status in the "Trial disposition (Completion/Discontinuation)" eCRF page). The primary reason for study discontinuation (derived from the 'Trial Disposition (Completion/Discontinuation)' eCRF page) will also be shown, and any COVID-19 related reasons (categorized as AE, death or other) will be included.
- Participants who started selexipag in the OLEP (with at least one record collected in "Study Drug Administration for Selexipag – Open Label Treatment" eCRF page).
- Participants who prematurely discontinued DB study intervention derived as all participants with 'Premature Discontinuation' selected for 'What was the reason for treatment end?' in the 'Study Drug Administration for Selexipag or Placebo - Double Blind Treatment' eCRF page. The 'primary reason for treatment discontinuation', derived from the 'Treatment Disposition

(End of Treatment)' eCRF page will also be shown, and any COVID-19 related reasons (categorized as AE, death or other) will be included.

- Participants who completed the DB treatment period (with 'Completed as per protocol' ticked as reason for treatment end in the "Study Drug Administration for Selexipag or Placebo - Double Blind Treatment" eCRF form).

Table 13 summarizes the above-described disposition categories by analysis timepoint:

Table 13: Disposition Information

Disposition category	Analysis set	by	Final analysis at end of DB period of the study (Analysis 3)
Screened	SCR	all	✓
Re-screened	SCR	all	✓
Screening failures	SCR	all	✓
Ongoing screening	SCR	all	✓
Randomized	FAS	by int	✓
Treated/Started DB study intervention	FAS	by int	✓
Prematurely discontinued DB study intervention before Analysis 3 time point	FAS	by int	✓
Completed DB study intervention	FAS	by int	✓
Prematurely discontinued the study	FAS	by int	✓
Started selexipag in the OLEP	FAS	by int	✓

int = intervention

Listings of participants will be provided for the following categories:

- Screening failures, based on the SCR set. This listing will include the primary reason for screen failure (taken from the 'Trial Disposition (Completion/Discontinuation)' eCRF page).
- Participants who prematurely discontinued study intervention during the DB period, along with the reason for premature discontinuation (taken from the "Treatment disposition (End of Treatment)" eCRF page). The listing will include participants who prematurely discontinued study intervention due to COVID-19, with the primary reason indicated as COVID-19, along with the specific reason (categorized as AE, death or other). The listing will be based on the SAS.
- Participants who prematurely discontinued the study before the EDBT along with the reason for premature discontinuation (taken from the "Trial Disposition" eCRF form). The listing will include participants who prematurely discontinued the study due to COVID-19, with the primary reason indicated as COVID-19, along with the specific reason (categorized as AE, death or other). The listing will be based on the FAS.
- Participants who were unblinded during the study, if any. The listing will be based on the SAS.

Time to premature DB study intervention discontinuation

Time from randomization to premature discontinuation of DB study intervention will be expressed in days and calculated as the date of premature discontinuation of DB study intervention minus date of randomization + 1 day or, for censored participants, as censoring date minus date of randomization + 1 day. Participants who discontinue DB study intervention prematurely (as

derived above) will be considered an 'Event' and their date of premature discontinuation will be used in the time to event calculation. Participants who did not prematurely discontinue DB study intervention will be censored at the date of last dose of DB study intervention.

Time to DB study intervention discontinuation will be descriptively summarized with Kaplan-Meier (KM) estimates on the SAS for each intervention group, overall and by age cohort.

6.2. Appendix 2 Demographics and Baseline Characteristics

All participant listings will be based on the FAS and sorted by intervention group, age cohort, site number, and participant number, unless otherwise specified.

The number of participants in each analysis set will be summarized by intervention group, overall, at randomization. The percentage of 'Participants included' and 'Participants excluded' from each analysis set will be based on the FAS. Reasons for exclusion of participants from analysis sets will also be included.

A listing of participants excluded from each analysis set will also be provided.

Participants' randomization information will also be listed, including the stratification variables as entered in the IWRS at the time of randomization.

In addition, the distribution of participants by region, country/territory, and site ID will be presented by intervention group, overall.

Table 14 presents a list of the demographic variables that will be summarized by intervention group, overall and by age cohort for the FAS (as well as by subgroup as described in Table 11).

All demographic data will be also reported in participant listings.

Table 14: Demographic Variables

Continuous Variables	**Summary Type**
Age at screening (years)	Descriptive statistics (N, mean (SD), median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Categorical Variables	**Summary Type**
Age categories at randomization (≥ 2 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years)	Frequency distribution with the number and percentage of participants in each category.
Body weight categories (≥9 to <25 kg, ≥25 to <50 kg, ≥50 kg)	
Tanner stage (1, 2, 3, 4, 5)	
Sex (Male, Female)	
Childbearing potential for female participants (Of childbearing potential, Premenarchal, Not applicable)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Not Reported)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)	

Geographical region (Asia, Eastern Europe, Latin America, North America, Western Europe)	

BMI is not collected in the eCRF and will be calculated as follows:

$$BMI = \frac{weight\ (kg)}{[height\ (m)^2]}$$

If weight is expressed in pounds (lb) it will be converted in kilograms using the formula:

$$weight(kg) = weight(lb) \times 0.45359237$$

If height is expressed in inches (in) it will be converted in meters (m):

$$height(m) = \frac{height(in) \times 2.54}{100}$$

Table 15 presents a list of the baseline disease characteristic variables that will be summarized by intervention group, overall and by age cohort for the FAS.

Table 15: Baseline Disease Characteristics Variables

Categorical variables	**Summary type**
PAH Etiology (Idiopathic PAH, Heritable PAH, aPAH-CHD, Drug and toxin induced PAH, PAH associated with HIV)	Frequency distribution with the number and percentage of participants in each category.
PAH Sub-Etiology[$] [PAH with co-incidental CHD, Post-operative PAH (persisting / recurring / developing >=6 months after repair of CHD)]	
Down syndrome (Present, Absent)	
WHO FC as per eCRF (I, II, III, IV) at baseline[*]	
Panama functional class (I, II, IIIa, IIIb, IV) at baseline[*]	
Continuous Variables	**Summary Type**
Time from PAH diagnosis (days)	Descriptive statistics (N, mean, SD, median and range [minimum and maximum]).
Time from first PAH symptoms (days)	

[*]See definition in Section 4.4.5/4.4.8
[$]For those participants in the aPAH-CHD category in PAH Etiology

All baseline variables are taken from the corresponding eCRF pages.

Time from PAH diagnosis/first PAH symptoms (days) is defined as the time from PAH diagnosis/first PAH symptoms to randomization.

Down syndrome will be considered as 'Present', if 'Trisomy 21' is present in the Medical History conditions/events in the 'General Medical History' eCRF form.

All baseline disease characteristic data will be also reported in participant listings.

An additional listing will show signs and symptoms of PAH at baseline (as recorded in the corresponding eCRF page).

6.2.1. Stratification Variables

Stratification variables are described in Section 1.2.3.1 and are:

- WHO FC (II vs III) at randomization, and
- PAH-specific therapy (monotherapy vs combination therapy) at randomization.

The stratification variables will be summarized (on the FAS) by intervention group, overall, as entered in the IWRS system by the investigator during the randomization transaction and as entered in the eCRF at the time of randomization.

The stratification variables (as entered in the IWRS system and in the eCRF at the time of randomization) will also be listed.

6.3. Appendix 3 Protocol Deviations

In general, major protocol deviations (PD) may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study.

Participants with major PDs will be identified during the conduct of the study in an ongoing manner using a comprehensive list of criteria (documented on the Major Protocol Deviation Criteria Form) as indicated in the Cross-Pharma TV-SOP-04282: Identification and Management of Clinical Trial Issues and Protocol Deviations for the definition of major protocol deviations.

Prior to each analysis timepoint all deviations will be closed, final and locked in the clinical trial management system (CTMS) and participants with major PDs will be summarized by the following categories/codes (DVDECOD).

- Entered but did not satisfy criteria (participant randomized but did not satisfy the inclusion/exclusion selection criteria)
- Received a disallowed concomitant treatment (participant took a forbidden concomitant medication)
- Received wrong treatment or incorrect dose (participant received wrong study intervention or incorrect dose)
- Developed withdrawal criteria but not withdrawn (participant developed withdrawal criteria during the study but was not withdrawn)
- Other (as per the full list on the study specific Major Protocol Deviation Criteria Form, including rescue treatment bosentan add-on therapy deviation)

The specific major PDs that will lead to exclusion from PPS are documented in the Major Protocol Deviation Criteria Form.

Major PDs will be summarized by category, displaying counts and percentages of participants with at least one major PD by intervention group, overall, by region and center (on the FAS). This summary table will be sorted, within each category, by descending overall frequency; if a tie occurs, the tied characteristics will be sorted alphabetically.

Listings will also be provided for:

- Participants with major PDs (by region and center)
- Participants with major PDs leading to exclusion from PPS, on the FAS
- Participants who received the incorrect intervention or dose (by region and center)
- Participants who did not meet inclusion criteria or who met exclusion criteria (by region and center).

Major COVID-19 related PDs, identified with the text 'COVID-19-related' as a prefix of the PD description, will be included in the PD summaries above. Additionally, both major and minor PDs related to COVID-19 will be listed separately (by region and center). Similarly, PDs related to regional crisis identified with the text "regional crisis" as a prefix of the PD description will be listed.

6.4. Appendix 4 Medical History

Participant medical history/current medical conditions based on the investigator's judgment (eg, serious past disease/conditions, chronic and ongoing acute disease/conditions) present before and/or still ongoing at the time of signing the ICF are recorded in the 'General Medical History' eCRF page.

The verbatim terms used in the eCRF reported by investigators to identify medical history events will be coded using the MedDRA.

The number and percentage of participants will be summarized by intervention group, overall and by age cohort, on the FAS, by SOC and PT, in descending order of frequency in the SOC and PT in the selexipag intervention group.

A listing of medical history data will also be provided based on the FAS.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications (ie, concomitant with DB study intervention) are collected in the 'Concomitant Therapy' eCRF pages and the original (verbatim) terms used by the investigators will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD).

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention, ie, any therapy for which the end date is prior to the DBSD (see Section 4.1.3).

Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention as summarized below:

- Start date on or after the DBSD and before or on DBED.

- Start date before the DBSD, and end date on or after it.
- 'Started prior to first study intervention intake' ticked and end date on or after DBSD.

Imputation rules for missing or incomplete start or end dates are described in Section 4.1.12.

Summaries of prior and concomitant medications will be presented by intervention group, overall and by age cohort and separately by body weight group, by anatomical therapeutic chemical (ATC) class (ATC Level 3 and ATC Level 4) and standardized medication name. ATC classes will be sorted by descending order of frequency overall. If the frequencies of ATC class are the same, alphabetical order will be used. The same rule applies for PTs within ATC class. Summaries will be presented based on the FAS. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior and concomitant medications will also be listed based on the FAS.

In addition, concomitant medications of special interest will be presented (see Section 6.8 Appendix 8 for a list of PAH-specific therapies, which constitute the concomitant medications of special interest in this study).

PAH-specific therapies concomitant at baseline are defined as any PAH-specific therapy with a start date prior to the DBSD and end date on or after DBSD and will be summarized overall and by age cohort and separately by body weight group, on the FAS.

In addition, for all participants and for participants with a CEC-confirmed disease progression event, separate shift tables showing shifts from PAH-specific therapy concomitant at baseline to new class of PAH-specific therapy (not concomitant at baseline and initiated on or after DBSD) will be presented overall, on the FAS. The possible categories included will be:

- Treatment with ERAs monotherapy
- Treatment with either PDE-5 inhibitor monotherapy or soluble guanylate cyclase stimulator (sGCs) monotherapy
- Treatment with prostacyclin/analogues/IP-agonist
- Treatment with combination of both ERAs and either PDE-5 inhibitor or sGCs
- Treatment with combination of ERAs, either PDE-5 inhibitor or sGCs and prostacyclin/analogs/IP-agonist (only allowed at disease progression)

PAH-specific therapies concomitant at disease progression are defined as any PAH-specific therapy with a start date prior to the day of the disease progression (defined as the primary endpoint date - 1) and an end date on or after it.

6.5.1. COVID-19 Infection Medications

Concomitant medications taken for COVID-19 infection will be summarized on the FAS. Medications within a specified class or category will be tabulated in the table using a standardized

medication name. Concomitant medications are not directly identifiable from the SDTM, they will be selected based on the AE they are linked to: if the related AE contains 'COVID-19' term then the medication is considered as taken for COVID-19 infection.

Concomitant medications for COVID-19 infection will also be listed (on the FAS).

6.6. Appendix 6 Compliance

6.6.1. Intervention Compliance

Study intervention compliance is based on study intervention accountability collected on the "Medication Kit Dispensation / Accountability [IWRS] - Selexipag or Placebo - Double Blind Treatment" eCRF page.

If the assigned study intervention was not dispensed to a participant, the following reasons are collected:

- Medication kit not available or damaged
- Other medication kit dispensed in error
- Study Medication Discontinued
- Visit Skipped or Administration Skipped
- Other

Compliance at each accountability (study intervention return) visit (expressed as %) will be calculated as follows:

100 x (amount of intervention dispensed - amount of intervention returned at Visit XX)/amount of intervention that should have been taken up to Visit XX), as per the Exposure log (up to date of returned at Visit XX in the Drug Accountability eCRF.

Compliance at 6 months (expressed as %) is calculated as:

100 x [total amount of intervention dispensed up to Visit 7 (Week 24) - total amount of intervention returned up to Visit 7 (Week 24)] / total amount of intervention that should have been taken up to Visit 7 (Week 24), as per the Exposure log (up to date of returned at Visit XX in the Drug Accountability eCRF.

Overall intervention compliance (expressed as %) is calculated as:

100 x (total amount of intervention dispensed up to the last visit of the participant - total amount of intervention returned up to the last visit of the participant) / total amount of intervention that should have been taken up to the last visit of the participant, as per the Exposure log (up to date of returned at Visit XX in the Drug Accountability eCRF.

The amount of intervention that should have been taken will be calculated on a participant basis, based on the investigator's prescription.

If 'Was drug accountability performed for returned study treatment?' is indicated as 'No' on the eCRF for any bottle of tablets at an accountability visit, compliance will not be calculated at that visit and that visit will be excluded from the overall calculation of compliance.

Compliance will be summarized descriptively at each accountability visit as a continuous variable for participants in the SAS, by intervention group, overall and by age cohort. The number and percentage of participants who had less than 60%, 60% to less than 80%, 80% to 120% and greater than 120% study intervention compliance through the first 6 months and overall intervention compliance will also be included in the summaries, along with the continuous variable summaries for both time intervals.

A listing of study intervention compliance will also be provided.

In addition, if after PAH-progression, participants are eligible for rescue treatment with bosentan in the context of this study, they will receive the pediatric dispersible oral formulation. Bosentan dispensation and accountability information during the DB treatment period is recorded on the "Medication Kit Dispensation/ Accountability [IWRS] - Bosentan - Double Blind Treatment" eCRF page.

Bosentan compliance will be listed.

6.6.2. Study Assessment Compliance

Study assessment compliance will be summarized based on the FAS, by intervention group, overall:

- Median follow-up time (months), defined as (LTV date - DBSD + 1) / 30.4375
- % of participants who missed at least one scheduled PAH signs/symptoms assessment
- % of participants who missed 2 or more consecutive scheduled PAH signs/symptoms assessments
- # of missed PAH signs/symptoms assessments per participant
- % of participants who missed at least one scheduled WHO FC assessment
- % of participants who missed 2 or more consecutive scheduled WHO FC assessments
- # of missed WHO FC assessments per participant
- % of participants who missed at least one scheduled vital signs assessment
- % of participants who missed 2 or more consecutive scheduled vital signs assessments
- # of missed vital signs assessments per participant
- % of participants who missed at least one scheduled hematology assessment
- % of participants who missed 2 or more consecutive scheduled hematology assessments
- # of missed hematology assessments per participant
- % of participants who missed at least one scheduled chemistry assessment

- % of participants who missed 2 or more consecutive scheduled chemistry assessments
- # of missed chemistry assessments per participant
- % of participants who missed at least one scheduled thyroid markers assessment
- % of participants who missed 2 or more consecutive scheduled thyroid markers assessments
- # of missed thyroid markers assessments per participant

For the % and # rows above, a subcategory will be included for assessment(s) "…due to COVID-19".

Study assessment compliance will also be listed, based on the FAS.

6.7. Appendix 7 Adverse Events of Special Interest

The following categories of AESI have been considered as either potential/identified important risks in the selexipag Core RMP or otherwise represent an event of interest for this study. These have been reported in selexipag studies, based on the SMQs/PTs in the current MedDRA version.

Any modifications of terms (according to the MedDRA SMQs/PTs) may occur based on later dictionary updates and/or external guidance and the latest definitions will be used at the time of the respective analyses.

Details will be provided in an AESI definition file (aesixxx.xlsx) that is saved at the selexipag compound level and version controlled in the SPACE Integrated Clinical Environment (or equivalent system).

- Anaemia
- Hypotension
- Hyperthyroidism
- Pulmonary venoocclusive disease associated with pulmonary oedema
- Bleeding events
- Renal function impairment / acute renal failure
- Major adverse cardiovascular events (MACE)
- Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
- Ophthalmological effects associated to retinal vascular system
- Light-dependent non-melanoma skin malignancies
- Medication errors

Other events of interest:

- Pregnancy
- Prostacyclin-associated reactions

- COVID-19 Infection

6.8. Appendix 8 Medications of Special Interest: PAH-Specific Therapies

PAH-specific therapies (except study intervention) are also collected in the 'Concomitant Therapy' eCRF pages and are identified by PTs including the following terms: "Ambrisentan", "Bosentan", "Sitaxentan", "Macitentan", "Sildenafil", "Tadalafil", "Vardenafil", "Udenafil", "Riociguat", "Iloprost", "Epoprostenol", "Treprostinil", "Beraprost". The following categories of treatments are defined:

- Treatment with ERAs monotherapy – identified by PTs including the following terms ("Ambrisentan" OR "Bosentan" OR "Sitaxentan" OR "Macitentan") AND NOT ("Sildenafil" OR "Tadalafil" OR "Vardenafil" OR "Udenafil") AND NOT "Riociguat".
- Treatment with PDE-5 inhibitor monotherapy or soluble guanylate cyclase stimulator monotherapy – identified by PTs including the following terms ("Sildenafil" OR "Tadalafil" OR "Vardenafil" OR "Udenafil" OR "Riociguat) AND NOT ("Ambrisentan" OR "Bosentan" OR "Sitaxentan" OR "Macitentan").
- Treatment with combination of both ERAs and either PDE-5 inhibitors or soluble guanylate cyclase stimulator – identified by PTs including the following terms ("Ambrisentan" OR "Bosentan" OR "Sitaxentan" OR "Macitentan" OR "Riociguat") AND ("Sildenafil" OR "Tadalafil" OR "Vardenafil" OR "Udenafil").
- Treatment with prostacyclin/analogs/IP-agonist (irrespective of treatment with ERAs or PDE-5 inhibitors or "Riociguat") – identified by PTs including the following terms "Iloprost" OR "Epoprostenol" OR "Treprostinil" OR "Beraprost" OR "Selexipag".

No treatments as defined in the bullet points above (it is not expected because the inclusion criteria require the presence of at least 1 PAH-specific background treatment for all participants).

6.9. Appendix 9 Marked Abnormal Laboratory Values

The following marked laboratory abnormalities will be used.

Hematology (SI units)

Laboratory test name	LL	LLL	HH	HHH
Hemoglobin (g/L)	<100	<80	Increase (> 20 g/L) above ULN or above baseline if baseline is above ULN	Increase (> 40 g/L) above ULN or above baseline if baseline is above ULN
Hematocrit (L/L)	<0.28 F <0.32 M	<0.20	>0.55 F >0.60 M	>0.65
Platelet count (10^9/L)	<75	<50	>600	>999
Leukocyte count WBC (10^9/L)	<3.0	<2.0	>20.0	>100.0

NA = Not applicable; ULN = upper limit of normal; WBC = white blood cells.

Blood Chemistry (SI units)

Laboratory test name	LL	LLL	HH	HHH	HHHH
Alanine Aminotransferase; ALT or SGPT (U/L)	NA	NA	≥ 3 × ULN	≥ 5 × ULN	≥ 8 × ULN
Aspartate Aminotransferase; AST or SGOT (U/L)	NA	NA	≥ 3 × ULN	≥ 5 × ULN	≥ 8 × ULN
Alkaline Phosphatase (U/L)	NA	NA	≥ 2.5 × ULN	≥ 5 × ULN	NA

Bilirubin; Direct Bilirubin	NA	NA	≥ 2 × ULN	≥ 5 × ULN	NA
Creatinine (µmol/L)	NA	NA	> 1.5 × ULN or > 1.5 × baseline if baseline is above ULN	> 3 × ULN or > 3 × baseline if baseline is above ULN	NA
Glucose (mmol/L)	<3.0	<2.2	>8.9	>13.9	NA
Sodium (mmol/L)	NA	<130	>150	>155	NA
Potassium (mmol/L)	<3.2	< 3.0	>5.5	>6.0	NA
Calcium (mmol/L)	<2.0	<1.75	>2.9	>3.1	NA
Urea Nitrogen	NA	NA	>2.5 × ULN	>5 × ULN	NA

NA = Not applicable, ULN = Upper limit of normal.

Thyroid parameters of interest (SI units)

Laboratory test name	LL	LLL	HH	HHH
Thyrotropin/TSH	< LLN for age	-	>ULN for age	-
Thyroxine; Free T4	<LLN for age	-	>ULN for age	-
Triiodothyronine; Free T3	<LLN for age	-	>ULN for age	-

LLN = lower limit of normal, ULN = Upper limit of normal.

Other parameters of interest

Laboratory test name	LL	LLL	HH	HHH
Pregnancy test	-	-	-	positive

6.10. Appendix 10 Endpoints for Analysis Timepoints

The following table details the endpoints presented for Analysis 1 and Analysis 2 and those to be presented for Analysis 3:

Endpoint	Analysis 1*	Analysis 2		Analysis 3	
		Overall	By Subgroup **	Overall	By Subgroup**
Time to CEC-confirmed disease progression	x	x	x	x	x
Change in log2(NT-proBNP) from baseline to Week 24	x*	x***	x	x***	x
Time to CEC-confirmed D/H due to PAH	x	x		x	
Time to death (all causes)	x	x		x	
Time to first CEC-confirmed hospitalization due to PAH	x	x		x	
Time to CEC-confirmed death due to PAH	x	x		x	
Time to clinical worsening	x	x		x	
WHO FC	x	x		x	
Change in exercise capacity	x	x		x	
Change in physical activity	x	x		x	
Panama FC	x	x		x	
NT-proBNP (absolute values, change from baseline and ratio of analysis visit/baseline)	x	x		x	
Change in echocardiography	x	x		x	
Quality of Life	x	x		x	

Palatability of Study Intervention	x	x		x	
Acceptability of Study Intervention	x	x		x	
Right Ventricular Failure 5-criteria Severity Score (RVf-severity score)		x****		x****	
Extent of exposure	x	x		x	
AEs/Deaths	x	x		x	x
Clinical Laboratory tests	x	x		x	
Vital Signs and Growth	x	x		x	
ECG	x	x		x	
Sexual Maturation (Tanner Stage) and Childbearing Potential	x	x		x	
RHC	x	x		x	
Health Economics		x		x	

*Descriptive only.
**Subgroups (See Table 11) considered for Analysis 2 and Analysis 3.
***Inferential. All other endpoints are descriptive.
****Post-hoc analysis.

The table below provides a summary of differences at analysis timepoints 1 and 3 compared to Analysis 2:

Analysis Timepoint	**Summary of Differences Compared to Analysis 2 with Rationale**
Analysis 1	• Descriptive statistics only. • NT-proBNP: No inferential analyses, no imputation for missing data • No subgroup analyses other than by age cohort were planned due to the small sample size (n=80). • Health economics variables were not defined. • Analyses based on the PPS not in scope.
Analysis 2	• Not Applicable
Analysis 3	• 140/439 outputs removed: • Outputs not required for clinical interpretation. • By age cohort summaries not required for clinical interpretation and/or too few participants or events. • Plots: where table is available. • Tables: where listing is sufficient due to few events. • Listings: where none in Analysis 2 and not expected to change in Analysis 3. •Analyses and summaries on PPS (except NT-proBNP): since very few participants (n=5) excluded from the PPS. • Efficacy: Sensitivity/Supplementary/NT-proBNP exploratory responder analyses where not required for clinical interpretation. • Safety: Time to death up to DBED + 30 days since already included in efficacy analyses. • 9/439 outputs replaced: • Summaries of inclusion and exclusion criteria replaced by listings as very few cases (TSIDEV02ovr and TSIDEV02age: 6 pts didn't meet inclusion and 0 met exclusion). • Summary of 6MWD by age cohort (TEFEXSMW01age) replaced with forest plot including age cohort and other prespecified subgroups as post-hoc analysis. • Tanner Stage summaries over time and Shift from baseline to each visit

	(TSFSXMT01ovr, TSFSXMT01age, TSFSXMT02ovr, TSFSXMT02age) replaced with post-hoc tables summarising to last assessment. • Childbearing potential summarized over time (TSFCHLD01ovr and TSFCHLD01age) replaced with shift tables from baseline to last available assessment. • Added clarifications for time period of interest for efficacy and safety analyses to determine DB treatment-emergent and time to event/censoring to consider participants who have initiated OL intervention. • Added details of the RVf-severity score and analyses as implemented post-hoc for Analysis 2. • Added tables of TEAEs and TESAEs by body weight group.

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