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

Selexipag / ACT-293987/ JNJ-67896049

Pulmonary arterial hypertension

Protocol AC-065A203

A prospective, multicenter, open-label, single-arm, Phase 2 study to investigate the safety, tolerability and pharmacokinetics of selexipag in children with pulmonary arterial hypertension

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7, Protocol Version 8	30 Sep 2021
COVID-19 Appendix Version 2 (EDMS-RIM- 263660, 5.0)	19 May 2021
Amendment 6, Protocol Version 7	19 May 2021
Amendment 5, Protocol Version 6	05 Oct 2020
COVID-19 Appendix Version 1 (EDMS-RIM- 263660, 1.0)	16 Jun 2020
Amendment 4, Protocol Version 5	18 Mar 2020
Amendment 3, Protocol Version 4	06 May 2019
Amendment 2, Protocol Version 3	01 Mar 2019
Amendment 1, Protocol Version 2	17 Sep 2018
Original Protocol	25 Jan 2018

Amendment 7 (30 September 2021)

Overall Rationale for the Amendment: To include an optional pharmacokinetic (PK) interim analysis 3 including data from age Cohort 3. If supported by the results, this will allow for confirmation of a dosing recommendation with fewer than 15 PK evaluable participants in Cohort 3 and enrollment in Cohort 3 can be stopped earlier.

The updates are indicated in bold for new text and in strikethrough for deletion in the following table.

Section Number and Name	**Description of Change**	**Brief Rationale**
PROTOCOL SYNOPSIS AC-065A203- (Design)	Statement was revised as follows: 'The selection of the dosing regimen for the Phase 3 study will be based on the safety, tolerability, and PK results evaluated in the interim ~~PK analyses (interim 1 and 2) and~~ **or** final PK analysis **(as applicable)**.	To adjust for the added optional third interim analysis.
3.1. Study design	Description of an optional third interim PK analysis including criteria for a dose confirmation with a sample size of fewer than 15 PK evaluable participants in Cohort 3 was added.	Given the rareness of pediatric pulmonary arterial hypertension (PAH), combined with the ongoing global Corona Virus Disease-2019 (COVID-19) pandemic, it has proven difficult to enroll participants in age Cohort 3 (≥ 2 to < 6 years of age). The option of confirming the selexipag dosing for participants in this age cohort based on the results of fewer than 15 PK evaluable Cohort 3 participants, was introduced.

Section Number and Name	Description of Change	Brief Rationale
5.1.4. Study drug starting dose and up-titration	Text was amended as follows: 'At any time during study treatment, study drug interruptions (eg, missed doses for any reason) of 3 days or more ~~(but less than 2 weeks, refer to Section 5.1.8)~~ will require a new up-titration according to the scheme from Day 1.'	In this Phase 2 study with only exploratory efficacy assessments, re-uptitration of study treatment is appropriate even after interruption >14 days, given that the investigators deem continued treatment with selexipag as appropriate for a given patient.
5.1.8. Study treatment dose adjustments and interruptions	Text was amended as follows: '~~Study treatment interruptions exceeding 2 consecutive weeks must lead to~~ **In case of** permanent discontinuation ~~off~~**from** study treatment ~~. In that case~~, the EOT visit must occur within 7 days of the discontinuation criterion being met.'	
9.2.5. Reporting procedures	Updated information about reporting of suspected unexpected serious adverse reaction (SUSAR) as follow: 'Any SAE that is assessed as related and unexpected against the RSI is known as a suspected unexpected serious adverse reaction (SUSAR) and ~~must be reported by the Sponsor to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs, and investigators.~~ **the sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.'**	To align with Janssen safety reporting process.
10.2.1.1. PK analysis and modeling	Text was amended as follows: 'More details will be described in modeling data analysis plan, which will be finalized before the PK interim analysis 1 **and any updates thereof**.'	As the modeling data analysis plan will be updated to include the details of third interim analysis.

Section Number and Name	Description of Change	Brief Rationale
10.4. Interim analyses	Text was amended as follows: 'Additional assessments of PK profiles **and interim analyses** may be performed**, as deemed appropriate by the sponsor**.	To provide clarity on additional interim analysis.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
AE	Adverse event
aPAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
ASO	Arteriosclerosis
AUC	Area under the plasma concentration-time curve
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve over one dosing interval at steady-state
$AUC_{\tau,ss,combined}$	Combined exposure over one dosing interval at steady-state
b.i.d.	Twice daily
BP	Blood pressure
CES	Carboxylesterase
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Confidence limit
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum concentration at steady state
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
CTEPH	Chronic thromboembolic pulmonary hypertension
$C_{trough,ss}$	Trough concentration at steady state
CYP	Cytochrome P450
ECG	Electrocardiogram
Echo	Echocardiography
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End-of-Study

EOT	End-of-Treatment
EP_4	prostaglandin-E2 subtype 4
ERA	Endothelin receptor antagonist
EU	European Union
FAS	Full Analysis Set
FC	Functional class
GCP	Good Clinical Practice
GRIPHON	Prostacyclin (PGI2G) receptor agonist in Pulmonary arterial HypertensiON
HIV	Human immunodeficiency virus
i.v.	Intravenous(ly)
IB	Investigator's Brochure
IC	Intermittent claudication
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
iMTD	Individual maximum tolerated dose
iPAH	Idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator site file
LAP	Left atrium pressure
LAR	Legally authorized representative
LVEDP	Left ventricular end-diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary arterial pressure
NCA	Non-compartmental analysis
NT pro-BNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension

PAH-aCTD	Pulmonary arterial hypertension associated with connective tissue disease
PAWP	Pulmonary arterial wedge pressure
PDE-5	Phosphodiesterase type-5
PI	Principal investigator
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PT	Preferred term
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
PVRi	Pulmonary vascular resistance index
RHC	Right heart catheterization
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SIV	Site initiation visit
SOC	System Organ Class
SSc	Systemic sclerosis
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T_{max}	Time at which C_{max} is observed
TSH	Thyroid-stimulating hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
WHO	World Health Organization
WU	Wood units

PROTOCOL SYNOPSIS AC-065A203

TITLE	A prospective, multicenter, open-label, single-arm, Phase 2 study to investigate the safety, tolerability and pharmacokinetics of selexipag in children with pulmonary arterial hypertension
OBJECTIVES	**Primary objective(s)** The primary objective of the study is to confirm the selexipag starting dose(s), selected based on pharmacokinetic (PK) extrapolation from adults, that leads to similar exposures as adult doses in children from ≥ 2 to < 18 years of age with pulmonary arterial hypertension (PAH) by investigating the PK of selexipag and its active metabolite ACT-333679 in this population. **Secondary objectives** To evaluate the safety and tolerability of selexipag in children from ≥ 2 to < 18 years of age with PAH. **Other objectives** Other objectives are described in Section 2.3. and Section 2.4.
DESIGN	This is a prospective, multicenter, open-label, single-arm, Phase 2 study. Approximately 60 participants will be enrolled in three different age cohorts (based on age at Baseline / Enrollment / Visit 2) to obtain at least 45 participants with evaluable PK profiles: • Cohort 1: ≥ 12 to < 18 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles) • Cohort 2: ≥ 6 to < 12 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles) • Cohort 3: ≥ 2 to < 6 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles). The starting dose is based on body weight, using the data from the population PK model in the GRIPHON/AC-065A302 study targeting the exposure observed in adult participants with

	PAH at a starting dose of 200 µg [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014]. The continuous relationship between dose and body weight is used to define bodyweight categories and starting dose for each body weight category, such that on average the exposure (combined exposure over one dosing interval at steady-state [$AUC_{\tau,ss,combined}$]) will be comparable to that in a 70 kg adult but will not exceed the exposure in a 50 kg adult [Modeling and Simulation Report, Pediatric dose selection 2016]: • 100 µg for participants with a body weight from ≥ 9 to < 25 kg. • 150 µg for participants with a body weight from ≥ 25 to < 50 kg. • 200 µg for participants with a body weight ≥ 50 kg. The starting dose selection will be confirmed or adjusted after the completion of each age cohort by updating the population PK model (interim analysis). Enrollment will start with both Cohort 1 and Cohort 2 (participants ≥ 12 to < 18 and ≥ 6 to < 12 years of age, respectively). After completion of PK assessments in at least 15 participants from Cohort 1 at Week 12, the dose-exposure relationship will be established using a population PK model [Modeling and Simulation Report, Pediatric dose selection 2016]. The PK data from any participants in Cohort 2 who have completed their PK assessments at this time will be included in this first interim analysis. Results of this model-based analysis will be used to confirm or adjust the selexipag doses initially selected. Enrollment of Cohort 3 (participants ≥ 2 to < 6 years of age) will start once the appropriate doses have been confirmed through modelling and simulation in a second interim analysis of PK data from the participants older than 6 years of age (i.e., Cohorts 1 and 2) and, if there is no safety concern, based on Independent Data Monitoring Committee (IDMC) reviews. Finally, the PK data pooled from all three age cohorts will be modelled to allow dosing recommendations for all participants

	≥ 2 years of age. A final PK analysis will be prepared based on the overall PK and safety data up to Week 16 evaluation. The selection of the dosing regimen for the Phase 3 study will be based on the safety, tolerability, and PK results evaluated in the interim or final PK analysis (as applicable). Participants who discontinue treatment any time before the profile PK sampling day may be replaced within their age cohort.
PERIODS	The study consists of the following consecutive periods: **Screening period:** Lasts up to 6 weeks; starts with the signature of the informed consent form (ICF) and ends with the administration of the first study treatment dose. **Treatment period:** Starts from the first dose of study treatment at Baseline/Enrollment visit and ends on the day of the last dose of selexipag (End-of-Treatment [EOT] visit). This includes: • **Up-titration period:** From the first dose of study treatment until the participant reaches their individual maximum tolerated dose (iMTD). This period is estimated to last up to 12 weeks. • **Maintenance period:** **After Week 12:** the participants will continue study treatment at the same dose up to Week 16. **After Week 16:** study treatment will continue as long as it remains beneficial for the participant [see Section 3.1.2 for details]. **EOT visit:** this visit should be conducted within 1 week of the last dose of study treatment. The participant will then enter the Safety follow-up period. **Safety follow-up period:** Starts on the day after the last dose of study treatment and ends 30 days thereafter. This period ends with a phone call that indicates the End-of-Study (EOS).

PLANNED DURATION	Approximately 7 years from first participant, first visit to last participant, last visit.
SITE(S) / COUNTRY(IES)	Approximately 30 sites in 20 countries (planned).
PARTICIPANTS / GROUPS	Approximately 60 participants will be enrolled in three different age cohorts (based on age at Baseline / Enrollment / Visit 2) to obtain at least 45 participants with evaluable PK profiles: • Cohort 1: ≥ 12 to < 18 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles). • Cohort 2: ≥ 6 to < 12 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles). • Cohort 3: ≥ 2 to < 6 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles).
INCLUSION CRITERIA	1. Signed and dated ICF by the parent(s) or legally authorized representative AND assent from developmentally capable children. 2. Males or females between ≥ 2 and < 18 years of age (at Baseline / Enrollment / Visit 2) with weight ≥ 9 kg. 3. PAH diagnosis confirmed by a documented historical right heart catheterization performed at any time before participant's enrollment, and characterized by: Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg; and Pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg (in the absence of pulmonary vein obstruction and/or significant lung disease, PAWP can be replaced by left atrium pressure or, in the absence of mitral stenosis, by left ventricular end-diastolic pressure); and

	Pulmonary vascular resistance index > 3 Wood units × m^2. 4. PAH belonging to Nice 2013 Updated Classification Group 1 (including Down syndrome) and of one of the following etiologies: Idiopathic. Heritable. PAH associated with congenital heart disease: PAH with co-incidental CHD. Post-operative PAH (persisting / recurring / developing ≥ 6 months after repair of CHD). Drug or toxin induced PAH. PAH associated with HIV. PAH associated with connective tissue disease. 5. World Health Organization functional class (WHO FC) II to III. 6. Participants treated with an endothelin receptor antagonist and/or a phosphodiesterase type-5 inhibitor, provided that the treatment dose(s) has been stable for at least three months prior to enrollment, or participants who are not candidates for these therapies. 7. Females of childbearing potential must have a negative pregnancy test at Screening and at Enrollment and must agree to undertake monthly pregnancy tests and to use a reliable method of contraception (if sexually active) from Screening up to study drug discontinuation + 30 days (EOS).
EXCLUSION CRITERIA	**Etiology** 1. Participants with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease, and/or pulmonary capillary hemangiomatosis. 2. Participants with PAH associated with Eisenmenger syndrome.

	3. Participants with moderate to large left-to-right shunts[1]. 4. Participants with cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, univentricular heart, or pulmonary atresia with ventricular septal defect, as well as participants with Fontan palliation. 5. Participants with pulmonary hypertension (PH) due to lung disease and/or hypoxia. For participants with Down syndrome, exclusion of lung disease and hypoxia causing PH should be documented (eg, computed tomography scan, polysomnography, lung function tests). **Treatment and intervention** 6. Previous treatment with Uptravi® (selexipag) within 2 weeks prior to enrollment. 7. Participants having received prostacyclin (epoprostenol) or prostacyclin analogs[2] (i.e., treprostinil, iloprost, beraprost) within 2 months prior to enrollment or who are scheduled to receive any of these compounds during the trial. 8. Treatment with another investigational drug within 4 weeks prior to enrollment. 9. Treatment with strong and moderate inhibitors of CYP2C8 (eg, gemfibrozil, clopidogrel, deferasirox, teriflunomide) within 2 weeks prior to enrollment until the last dose of selexipag + 3 days. 10. Treatment with inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole) are prohibited from 2 weeks prior to enrollment and until the last dose of selexipag + 3 days. 11. Any PAH-related surgical intervention planned, or participants listed for organ transplantation related to PAH.

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

[2] Single administration of drugs used for acute vasodilator testing during the RHC procedure is allowed (eg, intravenous/inhaled prostacyclin or inhaled nitric oxide or oral sildenafil).

	12. History or current suspicion of intussusception or ileus or gastrointestinal obstruction, per investigator's judgment. **Baseline abnormalities** 13. Known concomitant life-threatening disease with a life expectancy < 12 months. 14. Uncontrolled thyroid disease, per investigator's judgment. 15. Hemoglobin or hematocrit < 75% of the lower limit of normal range. 16. 1[3] Moderate or severe hepatic impairment, eg, Child-Pugh Class B or C [4] [see Section 14.4 Appendix 4]. 17. Clinical signs of hypotension that, in the investigator's judgment, would preclude the initiation of a PAH-specific therapy. 18. Participants with severe renal insufficiency (estimated creatinine clearance < 30 mL/min or serum creatinine > 221 µmol/L). 19. Severe coronary heart disease or unstable angina as assessed by the investigator. 20. Myocardial infarction within the last 6 months prior to enrollment. 21. Decompensated cardiac failure if not under close supervision. 22. Severe arrhythmias as assessed by the investigator. 23. Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months prior to enrollment. 24. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH. **Pregnancy and breastfeeding**

[3] Sub numbering introduced to highlight change from previous protocol version.

[4] The assessment for hepatic impairment at Screening (Child Pugh Score, see Section 14.4 Appendix 4) must be fully documented for participants with hepatic impairment as part of medical history and clinical signs and evidence (from central and/or local lab) of hepatic impairment.

	25. Pregnancy (including family planning) or breastfeeding. **Other categories** 26. Known hypersensitivity to the investigational treatment or to any of the excipients of the drug formulations. 27. Drug or substance abuse, or any condition that, in the opinion of the investigator, may prevent compliance with the protocol or adherence to study treatment. 28. Loss of 250 mL or more of blood within 3 months prior to screening. 29. History or clinical evidence of any disease and/or existence of any surgical or medical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study treatment(s) (eg, cholecystectomy). 30. "Criterion deleted per Amendment 6."
STUDY TREATMENT	**Investigational treatment** Selexipag is supplied by the sponsor as child-proof bottles containing tablets for oral administration twice daily (b.i.d.) with the following dosage strengths: • Film-coated tablets containing 200 μg of selexipag. • Film-coated mini-tablets containing 50 μg of selexipag. Study medication administration will start in the evening of Day 1, and continue thereafter with b.i.d. dosing, i.e., once in the morning and once in the evening. During the up-titration period of 12 weeks, it is recommended that the doses are increased weekly in increments equal to the starting dose until the participants reach their iMTD, or until the maximum dose corresponding to their baseline weight category is achieved. To improve tolerability, it is recommended that the study drug, selexipag, is taken with food and, at the beginning of each up-titration phase, that the first increased dose is taken in the evening. Participants can take 200 μg tablets and 50 μg mini-tablets with soft food (i.e., yoghurt, apple sauce/puree/mousse or mashed banana). The 50 μg mini-tablets can also be dispersed in apple- or orange-juice. The maximum dose allowed will be 8-fold the corresponding starting dose:

	• Body weight category ≥ 50 kg: starting dose of 200 µg titrated up to the iMTD or the maximum of 1,600 µg b.i.d. • Body weight category ≥ 25 to < 50 kg: starting dose of 150 µg titrated up to the iMTD or the maximum of 1,200 µg b.i.d. • Body weight category ≥ 9 to < 25 kg: starting dose of 100 µg titrated up to the iMTD or the maximum of 800 µg b.i.d. Up-titration will be agreed upon during scheduled telephone calls or visits. At Week 12, the iMTD for each participant will be determined. This dose should be kept unchanged until Week 16. Body weight category, starting dose, and up-titration scheme determined at Baseline/Enrollment will be kept unchanged until Week 16. After Week 16, if the body weight category of the participant has changed, the study drug can be up-titrated further or down-titrated to the corresponding dose level of the next body weight category, if deemed appropriate by the investigator. In addition, irrespective of whether the body weight category changes or not, after Week 16 the investigator will be allowed to change the participant's study drug dose further if needed (up to the maximum allowed dose based on body weight category). If a participant has tolerability issues or experiences adverse reactions reflecting the mode of action for selexipag [see Section 5.1.10], the dose can remain the same without further up-titration (pause in up-titration). Up-titration can be resumed after the pause, or the dose can be reduced to the previous dose level. The decision to pause up-titration, to up-titrate or down-titrate study drug, or to permanently discontinue the study drug will be based on the investigator's medical judgment.
ENDPOINTS	**Primary pharmacokinetics endpoint(s)** The primary endpoint is model-based exposure ($AUC_{\tau,ss,combined}$) of selexipag and ACT-333679, corrected for their potency, determined during the 12-week up-titration period.

	Secondary pharmacokinetics endpoints • Area under the plasma concentration-time curve over one dosing interval at steady-state ($AUC_{\tau,ss}$), maximum concentration at steady state ($C_{max,ss}$), and the time at which $C_{max,ss}$ is observed ($t_{max,ss}$) for selexipag and ACT-333679, based on non-compartmental analysis (NCA). • Trough concentration at steady state ($C_{trough,ss}$) on Day 15, and at Weeks 4 and 6 (i.e., Visits 4, 5, 6) for selexipag and ACT-333679. **Safety endpoints** • Treatment-emergent adverse events (TEAEs) occurring up to EOT + 3 days. • Treatment-emergent serious adverse events (TESAEs) occurring up to EOT + 3 days. • Adverse events (AEs) leading to permanent discontinuation of study drug. • Treatment-emergent deaths (all causes) occurring up to EOT + 3 days. • Treatment-emergent marked laboratory abnormalities (hematology and blood chemistry tests) over time, occurring up to EOT + 3 days. • Change from baseline in selected hematology and blood chemistry laboratory parameters over time up to EOT + 3 days. • Treatment-emergent electrocardiogram (ECG) abnormalities over time, occurring up to EOT + 3 days. • Change from baseline in thyroid-stimulating hormone over time, up to EOT + 3 days. • Change from baseline in vital signs (blood pressure, heart rate) over time, up to EOT + 3 days. • Change from baseline in height and body mass index over time, up to EOT + 3 days.

	• Change from baseline in sexual maturation (Tanner stage) over time, up to EOT + 3 days. **Exploratory endpoints** • Change from Baseline/Enrollment up to each time point of assessment in modified New York Heart Association / WHO FC. • Change from baseline up to each time point of assessment in exercise capacity, as measured by the 6-minute walk distance (6MWD). • Change from baseline in Panama FC up to each time point of assessment. • Percent of baseline in plasma NT pro-brain natriuretic peptide at each time point of assessment. • Change from baseline up to each time point of assessment in echocardiographic variables (imaging and Doppler evaluation): Right ventricular systolic pressure. Tricuspid annular plane systolic excursion. Pulmonary artery acceleration time. Left ventricular eccentricity index. Right atrial area index (from apical 4 chamber view). Tricuspid annular diameter (from apical 4 chamber view). • Time to the first of the following disease progression events occurring between enrollment and EOT: 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 (i.e., shortness of breath/dyspnea, chest pain, cyanosis, dizziness/ near syncope, or fatigue), or ○ New occurrence or worsening of signs of right heart failure not responding to oral diuretics [§]excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (eg, pneumonia). *worsening from baseline. [#]eg, ERA, PDE-5 inhibitor, prostanoids, prostacyclin receptor (IP receptor) agonist, soluble guanylate cyclase stimulator. **Other endpoints** • Palatability of selexipag formulation at Day 1, Week 12, and EOT, assessed using a 5-point facial hedonic scale. • Acceptability of selexipag formulation at Day 1, Week 12, and EOT, as assessed through a 3-point categorical scale determining whether the child swallowed the medication.
ASSESSMENTS	Refer to the schedule of assessments in Table 4 and Table 5.
STATISTICAL METHODOLOGY	**Analysis Sets** The Screened Analysis Set includes all participants who are screened and have a participant identification number. The Full Analysis Set includes all enrolled participants who were eligible to receive the study drug. The Pharmacokinetic Analysis Set comprises all participants included in the Safety Set who complied with the protocol sufficiently and did not deviate from the protocol in a way that might affect the PK outcome of the study. Criteria for sufficient compliance include exposure to treatment, availability of PK

	measurements, and absence of major protocol deviations that have an impact on the PK. The Safety Analysis Set includes all participants who received at least one dose of study treatment. The observed PK data will be described by a population PK model using the same model structure as for the adult participants with PAH in the GRIPHON study [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014, Modeling and Simulation Report, Pediatric dose selection 2016]. This population PK model describes the PK of selexipag and ACT-333679 by 2-compartmental distribution models with linear elimination. Selexipag is absorbed by a first-order process and part of the elimination from the central compartment is a metabolic transformation to form ACT-333679 [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014]. **Analysis of secondary PK variable(s)** Plasma concentrations will be summarized per time point, by dose and body weight cohort using arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and two-sided 95% confidence interval (CI) of the mean. $AUC_{\tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$, and $t_{max,ss}$ for selexipag and ACT-333679 based on NCA for selexipag and ACT-333679 will be listed and summarized by dose and body weight cohort, with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, coefficient of variation in %, and 95% CI of the arithmetic and geometric means. Dose proportionality for $AUC_{\tau,ss}$ and $C_{max,ss}$ of selexipag and ACT-333679 will be explored by the power model as described by [Gough 1995]. **Safety variables**

	All analyses of safety variables will be carried out descriptively using the Safety Analysis Set, consisting of all treated participants, and will be performed as follows: • in the overall population. • by iMTD dose groups. • by age cohort. The number and percentage of participants with at least one TEAE / TESAE / AE leading to study treatment discontinuation will be described by system organ class (SOC) and preferred term (PT) up to EOT + 3 days, and separately for the up-titration period (until Week 12) and the maintenance phase (> Week 12 until EOT + 3 days). The same analysis will be performed according to the maximum intensity of reported AEs and their relationship to the study drug. The number and percentage of treatment-emergent deaths will be described by SOC and PT up to EOT + 3 days. For each laboratory and ECG variable, the number and percentage of participants with at least one treatment-emergent marked abnormality will be summarized up to EOT + 3 days. Vital signs and sexual maturation variables will be summarized over time up to EOT + 3 days, using descriptive statistics for continuous variables.
STUDY COMMITTEES	An IDMC has the overall responsibility for safeguarding the interests of participants by monitoring safety data obtained in the study and by making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with the highest scientific and ethical standards. The PK results of the interim analyses (after completion by Cohorts 1 and 2, and final PK results of all three cohorts) will be provided to the IDMC for review, if requested by the committee. The IDMC will be fully operational prior to enrollment of the first participant into the study. The

	composition and operation of the IDMC is described in the IDMC charter.

PROTOCOL

1 BACKGROUND

1.1 Indication

Pulmonary arterial hypertension (PAH) in children.

1.1.1 Definition and diagnosis

PAH is a rare, progressive and eventually fatal disease, characterized by vasoconstriction and progressive remodelling of pulmonary arteries leading to increased resistance to blood flow in the pulmonary circulation, right ventricular failure, and death. With regards to the definition, pathophysiology, symptoms, and response to PAH-specific medicines, PAH disease in children shares similarities with adult PAH [Barst 2011].

The definition of PAH in adults and children is the same and is based on pulmonary hemodynamics measured by right heart catheterization (RHC): a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest demonstrates pulmonary hypertension (PH). In patients with PAH, the PH is pre-capillary; thus, they have a normal pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and an elevated pulmonary vascular resistance (PVR) > 3 Wood units (WU) (mmHg/L·min) [Hoeper 2013, Ivy 2013]. In children, PVR index (PVRi) is used instead of PVR in order to account for growth; PAH is defined as PVRi > 3 WU × m^2 [Ivy 2013, Abman 2015, Hansmann 2016].

PVRi [WU × m^2] mPAP [mmHg] PAWP [mmHg] / cardiac index [(L/min) / m^2]

cardiac index [(L/min) / m^2] cardiac output [L/min] / body surface area [m^2]

A PAH diagnosis can be confirmed only if elevated left heart pressures are excluded as a reason for PH. PAWP is used for this purpose as a surrogate for directly measured left atrial pressure (LAP) [Galiè 2015]. In the absence of mitral stenosis, left ventricular end diastolic pressure (LVEDP) can also be used as an alternative surrogate for LAP [Grignola 2011, Takala 2003].

Beyond the neonatal period, the pathology of pulmonary vascular disease is generally the same across all age ranges. The histopathological findings seen in adults with PAH are also observed in children. Both populations have vascular and endothelial dysfunction, and present at diagnosis with elevations in PVR and pulmonary artery pressure [Barst 2011]. The distribution between etiologies in pediatric PAH is different to that of adults. There are no indications from clinical experience that this translates into differences in response to PAH-specific medicines.

1.1.2 Classification

According to the revised clinical classification of PH [Simonneau 2013] PAH comprises: idiopathic PAH (iPAH); heritable PAH (hPAH); drug-and toxin-induced PAH; and PAH associated with connective tissue diseases (PAH-aCTD), HIV infection, portal hypertension, congenital heart disease (aPAH-CHD), and schistosomiasis; it also includes the subcategories pulmonary veno-occlusive disease [PVOD] and/or pulmonary capillary hemangiomatosis, as well as persistent pulmonary hypertension of the newborn [Ivy 2013].

This protocol addresses iPAH, hPAH, and aPAH-CHD with some restrictions in order to take into account information gathered from the GRIPHON study in adult patients with PAH. Patients with PAH associated with HIV, PAH-aCTD, and drug or toxin-induced PAH are also included in this trial, even though they represent only a minor proportion of the pediatric PAH population.

This protocol excludes patients with Eisenmenger syndrome, as well as patients with open left-to-right shunts.

1.1.3 Epidemiology

In the majority of pediatric patients, PAH presents as iPAH or aPAH-CHD [Ivy 2013]. A retrospective, nationwide registry-based study performed in the Netherlands from 1991 2005 revealed an annual incidence and point prevalence of 0.7 and 4.4 cases per million children for iPAH, and 2.2 and 15.6 cases per million children for aPAH-CHD, respectively [van Loon 2011]. In 2005, the estimated annual prevalence per million children in France was 2.2 cases of iPAH [Fraisse 2010]. Data from the UK National Pulmonary Hypertension Service between 2001 and 2007 showed that the incidence of iPAH was 0.48 cases per million children per year, and the prevalence was 2.1 cases per million children [Moledina 2010]. A US database study (2012 2013) published an annual incidence range of pediatric iPAH of 0.5 0.9 cases per million children-years, and a prevalence range of 4.4 6.0 cases per million [Li 2017].

1.1.4 Current treatment and unmet clinical need

The current management of pediatric PAH is based primarily on results from studies in adult patients, together with expert recommendations, such as those from the 5th World Symposium for Pulmonary Hypertension [Galiè 2013, Ivy 2013], which were recently adopted by the European Society of Cardiology and European Respiratory Society [Galiè 2015]. The treatment algorithm takes into account risk factors for mortality (clinical evidence of right heart failure, progression of symptoms, syncope, failure to thrive, functional class [FC] III and IV, b-type natriuretic [BNP] / N-terminal pro-BNP [NT pro-BNP], echocardiography [Echo], and hemodynamics) [Ivy 2016]. Consensus treatment guidelines recommend similar therapeutic algorithms in children (based on expert opinion) and adults (evidence-based) [Ivy 2013, Abman 2015, Hansmann 2016].

This applies to all PAH-specific medications, including prostacyclin and its analogs. Observational data with epoprostenol, the synthetic prostacyclin, showed similar effectiveness in children with PAH compared to adults with respect to improving survival and hemodynamics, and relieving symptoms [Barst 1996, Barst 1999, Yung 2004]. Prior to the development of PAH-specific therapies, the median survival of adult patients diagnosed with idiopathic PAH was reported to be approximately 2.8 years; the median survival of pediatric patients was 10 months [D'Alonzo 1991]. Yung et al. confirmed the significantly improved long-term survival in children with iPAH/hPAH treated with intravenous (i.v.) epoprostenol compared with children for whom i.v. epoprostenol was not available [Yung 2004]. Survival for all children treated with epoprostenol at 1, 5, and 10 years was 94%, 81%, and 61%, respectively. Doses of epoprostenol need to be gradually increased to the individually tolerated dose depending on the emergence of prostacyclin receptor-related side effects. Since the introduction of epoprostenol, the efficacy of this product in children with PAH using an up-titration regimen has been documented in clinical practice and in registries [Barst 2010]. The appropriateness of the up-titration concept when applied to selexipag was proven in the GRIPHON study. Despite this survival improvement, PAH remains a fatal disease. Therefore, there is an unmet clinical need for additional treatment options in children and earlier use of oral medication activating the prostacyclin pathway.

Similarity in treatment response between adult and pediatric patients has been observed in all classes of PAH-specific therapies, typically reflected in a 20% or greater reduction in PVR, a key pathophysiological characteristic of the disease. Similarity in treatment response between adults and children with PAH is also to be expected with the IP-receptor agonist selexipag, given the similar expression of IP receptors driving the pharmacological response in adults and children. Specifically, selexipag has been shown to be efficacious in adult patients with iPAH and aPAH-CHD, the most frequent etiologies in pediatric patients with PAH.

The expression of IP receptors is similar in smooth muscle cells from adult and pediatric patients. In particular, IP receptor expression in pulmonary arterial smooth muscle cells derived from lungs of adults and children with iPAH is reduced to approximately 65% of that observed in normal human lungs [Falcetti 2010]. As the potency and efficacy of selexipag and its active metabolite in inducing intracellular signaling (cyclic adenosine monophosphate production) correlate with the density of IP receptors [Gatfield 2016, Research Report ACT-333679 2014], it is anticipated that selexipag will have similar effects in target cells expressing comparable levels of IP receptors, irrespective of age, provided that other components of the signaling pathway remain unchanged.

1.2 Study treatment(s)

1.2.1 Introduction

Selexipag (ACT-293987) is an orally available, selective, and long-acting non-prostanoid agonist of the prostacyclin receptor (IP receptor) approved and commercially available for the treatment of adult patients with PAH in the US, the European Union, Japan, and other countries. Selexipag is currently under development for chronic thromboembolic pulmonary hypertension (CTEPH) and arteriosclerosis obliterans (ASO) with intermittent claudication (IC). Selexipag was approved in the US in December 2015 (brand name: Uptravi® [Uptravi® USPI]), and in Europe in May 2016 [Uptravi® SmPC].

1.2.2 Nonclinical data

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

The efficacy of selexipag after oral administration was demonstrated in several nonclinical models of systemic hypertension and PH. In a rat model of PH, selexipag preserved endothelial function, decreased mPAP and media thickening of pulmonary arteries, and diminished right ventricular wall hypertrophy. Selexipag treatment also led to significant improvement of survival [Selexipag IB, Section 1.2].

Unlike prostacyclin (PGI_2) analogs, selexipag and its active metabolite ACT-333679 bind to the human IP receptor with high selectivity over other prostanoid receptors. As shown in cellular assays, IP receptor activation by selexipag or ACT-333679 leads to vascular smooth muscle relaxation, anti-proliferation, and anti-fibrotic effects. Selexipag and ACT-333679 do not activate the molecular processes involved in desensitization of human IP receptors, avoiding receptor internalization and tachyphylaxis [Selexipag IB, Section 1.2].

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

In the repeat-dose toxicity studies in rodents, strong blood pressure decrease as a result of exaggerated pharmacology induced transient clinical signs, reduced food consumption, and body weight gain. In adult and juvenile dogs, intestine and bone / bone marrow were identified as the main target organs after treatment with selexipag. In dogs less than 1 year old, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. The effect occurred at 5-fold the human exposure (i.e., corrected for potency;

415-fold based on total exposure; active metabolite). Safety margins based on no-observed-adverse-effect levels for the active metabolite, corrected for difference in receptor potency between human and dog, were 2-fold (i.e., corrected for potency; 180-fold based on total exposure) in relation to human exposure at a dose of 1,600 µg of selexipag twice daily (b.i.d.). The intussusception did not occur in mouse or rat toxicity studies. Because of the species-specific propensity of dogs to develop intussusception and the safety margin, this finding is not considered relevant for adult humans. However, as young children are known to be prone to developing intussusception, the use of selexipag in children below 2 years of age is not recommended based on the nonclinical findings.

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

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

In the 2-year carcinogenicity studies, selexipag caused an increased incidence of thyroid adenomas in mice and Leydig cell adenomas in rats [Selexipag IB, Section 1.2]. The mechanisms are rodent-specific. The findings were observed at exposures that were more than 25-fold higher than the exposure in humans and are, therefore, not relevant for humans. Tortuosity of retinal arterioles was noted after 2 years of treatment only in rats [Selexipag IB, Section 1.2]. Mechanistically, the effect is considered to be induced by life-long vasodilation and subsequent changes in ocular hemodynamics. The finding is considered to be species-specific.

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

Selexipag and its active metabolite were phototoxic *in vitro*. A dedicated clinical study did not indicate any potential phototoxicity of selexipag in humans [Selexipag IB, Section 5.5.2.1].

1.2.3 Clinical data

1.2.3.1 Exposure

As of 20 June 2017, a total of 1,705 subjects have received one or more doses of selexipag in completed, clinically completed, or ongoing open-label clinical studies. This includes 510 subjects in clinical pharmacology studies, 1,065 patients with PAH, 32 patients with CTEPH, 62 patients with ASO, and 36 patients with Raynaud's Phenomenon secondary to

systemic sclerosis (SSc). In addition, a total of 262 subjects have been enrolled in the ongoing double-blind studies AC-065A308/TRITON, NS-304C P3-1, and NS-304A P2-2.

In Phase 1 studies, subjects received multiple doses of up to 1,800 µg b.i.d. of selexipag and the entire treatment duration was up to 24 days.

For a tabular summary of Phase 2 3 studies with selexipag, see the Investigator's Brochure (IB) [Selexipag IB, Section 1.3].

1.2.3.2 Pharmacokinetics and metabolism

The pharmacokinetics (PK) of selexipag and its active metabolite ACT-333679 were dose-proportional up to a single dose of 800 µg and multiple doses of up to 1,800 µg b.i.d. Steady-state conditions of selexipag and its active metabolite were reached within 3 days. No accumulation in plasma was observed.

Selexipag is rapidly absorbed and is hydrolyzed by carboxylesterase (CES) enzymes to its active metabolite. Maximum observed plasma concentrations of selexipag and its active metabolite after oral administration are reached within 1 3 hours and 3 4 hours, respectively. Oxidative metabolism primarily catalyzed by cytochrome P450 (CYP) 2C8 and to a smaller extent by CYP3A4 leads to the formation of hydroxylated and dealkylated products. Uridine 5'-diphosphoglucuronosyltransferase (UGT) 1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceed 3% of the total drug-related material [Selexipag IB, Section 5.2.2]. After oral administration, exposure at steady-state to the active metabolite in both healthy subjects and patients with PAH is approximately 3- to 4-fold higher than to the parent compound. In the presence of food, the exposure to selexipag after a single dose of 400 µg was increased by 10% in Caucasian subjects and decreased by 15% in Japanese subjects, whereas exposure to the active metabolite was decreased by 27% (Caucasian subjects) and 12% (Japanese subjects). In the presence of food, the time to reach maximum plasma concentration (t_{max}) of selexipag was delayed by approximately 1 1.5 h. More subjects reported adverse events (AEs) after administration in the fasted than in the fed state. Elimination of selexipag is predominantly via metabolism with a mean terminal half-life of 0.8 2.5 h. The active metabolite has a half-life of 6.2 13.5 h. The total body clearance of selexipag is, on average, 17.93 L/h. Excretion in healthy subjects was complete 5 days after administration and occurred primarily via feces (accounting for 93% of the administered dose) compared to 12% in urine. The absolute bioavailability of selexipag is approximately 49%.

Multiple-dose treatment with selexipag (800 µg b.i.d. and 1,600 µg b.i.d.) did not have an effect on cardiac repolarization in healthy subjects. No adjustment to the dosing regimen is needed in elderly patients. No clinically relevant effects of sex, race, disease severity, or body weight on the PK of selexipag and its active metabolite have been observed in PAH

patients. *In vitro* experiments showed that selexipag and ACT-333679 are highly bound to plasma proteins (> 99%) [In vitro Study ACT-293987A and ACT-333679A 2009].

1.2.3.3 Efficacy results in adult patients with PAH

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

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

Study NS-304/-02: This Phase 2a study in patients with PAH enrolled 43 patients who were randomized in a 3:1 ratio to selexipag (n 33) and placebo (n 10). Patients were up-titrated from the starting dose of 200 µg b.i.d. to a maximum of 800 µg b.i.d. based on the tolerability of each subject. All patients received either an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type-5 (PDE-5) inhibitor at baseline. After 17 weeks of treatment, a significant 30.3% reduction in PVR with selexipag compared with placebo (P 0.0045, Wilcoxon rank sum test, Per-protocol Set) was observed, as well as a mean treatment effect on 6MWD of 24.2 ± 23.7 meters (p 0.2218, Wilcoxon rank sum test, Per-protocol Set).

Study AC-065A201: This Phase 2, multicenter, uncontrolled, open-label study in Japan enrolled 37 patients with PAH who received selexipag. Patients were allowed to receive PDE-5 inhibitors and ERAs. Patients were up-titrated from the starting dose of 200 µg b.i.d. up to a maximum of 1,600 µg b.i.d. based on the tolerability of each subject. The maintenance dose for each patient was determined by Week 12 and maintained up to Week 16. The efficacy evaluation took place at Week 16 of treatment. Long-term treatment continued up to Week 144. Patients could be treated further at the investigator's request. After 16 weeks of treatment, the median change in PVR from baseline 120.9 dyn·sec/cm^5 (95% confidence limits [CLs]): 184.5, 59.5 dyn·sec/cm^5) was observed in the Per-protocol Set (two-sided p-value of the Wilcoxon signed rank test < 0.0001). The

geometric mean percentage ratio in PVR (Week 16/baseline × 100) was 79.7% (95% CLs: 74.0, 86.0). In a supportive analysis using the All-treated Set, similar results to those in the Per-protocol Set were observed. The long-term treatment phase of the study is currently ongoing.

For efficacy data from other completed or ongoing selexipag clinical studies in adult patients with PAH, CTEPH, Raynaud's Phenomenon secondary to SSc and ASO-IC, see the Investigator's Brochure (IB) [Selexipag IB].

1.2.3.4 Safety

1.2.3.4.1 Phase 1 studies

In the Phase 1 studies, selexipag was well tolerated after single doses of up to 400 µg (fasted, oral, or i.v.) and multiple daily oral doses of up to and including 1,600 µg b.i.d. (fed). The most frequent AEs were headache, myalgia, arthralgia, jaw pain, nausea, vomiting, diarrhea, and dizziness. No treatment-related effects of selexipag on electrocardiogram (ECG) morphology or cardiac repolarization were noted. There were no clinically relevant changes in vital signs, thyroid markers, or laboratory tests. No changes were observed in the platelet aggregation test, bone turnover, or coagulation markers. An exploratory Phase 1 study was performed to evaluate the photosensitizing potential of selexipag under steady-state conditions. The study did not indicate that selexipag has clinically relevant photosensitizing potential in humans. More subjects reported AEs after administration in the fasted state than in the fed state in the food effect study. In a study performed in subjects with impaired liver function, one serious related event of hepatic encephalopathy was reported. No further subjects with severe hepatic impairment (Child-Pugh C) were enrolled in the study. In the thorough QT study (AC-065-106), there was one serious adverse event (SAE) of symptomatic hypotension reported by a female subject following administration of multiple doses of selexipag (at 1200 µg dose). This event was severe in intensity and resolved without sequelae on the same day after discontinuation of study treatment.

1.2.3.4.2 Safety data from GRIPHON

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

7.1%, respectively). A total of 31.7% of patients in the selexipag group and 37.1% in the placebo group had at least one AE leading to discontinuation of study treatment. Other than prostacyclin-associated AEs, most of the AEs that led to discontinuation of study treatment were SAEs associated with the underlying PAH disease.

Overall, in the GRIPHON study, the nature and incidence of typical prostacyclin-associated AEs (i.e., headache, flushing, diarrhea, nausea, vomiting, jaw pain, myalgia, and arthralgia) on selexipag was largely in line with that observed with prostacyclin and prostacyclin analogs [Sitbon 2015; Selexipag IB Section 1.3.4]

Hypotension was reported more frequently in the selexipag group than in the placebo group (5.9% and 3.8%, respectively). In the selexipag group 9.7% of patients had systolic blood pressure (SBP) < 90 mmHg on at least one occasion, compared to 6.7% in the placebo group. A decrease from baseline of > 40 mmHg in SBP was reported for 2.3% and 3.0% of patients in the selexipag and placebo groups, respectively.

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

Bleeding was not observed more frequently in selexipag-treated patients compared to placebo, including in those patients treated concomitantly with anticoagulants. Anemia was reported more frequently in the selexipag group and a small reduction in hemoglobin was observed at most post-baseline visits.

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

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

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

Safety data from other completed selexipag clinical studies in adult patients with PAH, CTEPH, Raynaud's Phenomenon secondary to SSc, and ASO-IC show a safety profile consistent with that of the GRIPHON study [Selexipag IB]. Safety data in this study are

reviewed on an ongoing basis by the Independent Data Monitoring Committee (IDMC) (see Section 3.3).

1.3 Purpose and rationale of the study

The overall rationale for the development of selexipag in children with PAH is based on the robust and conclusive results of the pivotal study with selexipag in adult patients with PAH (GRIPHON/AC-065A302, N 1,156) demonstrating efficacy in delaying disease progression in adults [Sitbon 2015].

In the US, Uptravi is indicated for the treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

In Europe, Uptravi is indicated for the long-term treatment of PAH in adult patients with WHO FC II III, either as combination therapy in patients insufficiently controlled with an ERA and/or PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

The selection of the starting dose for pediatric participants is based on their body weight category, using the data from the population PK model in the GRIPHON study, targeting the exposure observed in adult PAH patients at a starting dose of 200 µg [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014].

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

The development plan of selexipag in children will consist of this Phase 2 study to establish the selexipag dose(s) and determine the PK of selexipag and its active metabolite, followed by a Phase 3 study to assess the efficacy, safety, and tolerability of selexipag in this population.

Therefore, the purpose of this study is to confirm the selexipag doses in children from ≥ 2 to < 18 years of age with PAH that lead to an exposure similar to that in adult participants. The selection of the selexipag starting dose is based on a PK extrapolation from adults to pediatric participants. In addition, the safety and tolerability of selexipag in children from ≥ 2 to < 18 years of age will be assessed.

1.4 Summary of known potential benefits and risks

1.4.1 Benefits

Selexipag, a non-prostanoid IP (prostacyclin) receptor agonist, is an orally available medicine with PK characteristics suitable for b.i.d. dosing.

The efficacy of selexipag in the treatment of adult patients with symptomatic PAH was demonstrated in GRIPHON, the largest (N 1,156) and only long-term (mean duration 1.5 years and up to 4.2 years), controlled outcome study conducted with an IP-receptor agonist. The treatment effect was consistent across WHO FC II III and was fully preserved in patients already treated with an approved PAH-specific medicine at baseline (80% of the study population), as well as in patients treated with two such medicines (30% of the study population).

GRIPHON was the first study to demonstrate the outcome benefit of an IP-receptor agonist, in particular when added sequentially to therapies acting on other pathogenic pathways in PAH (endothelin and nitric oxide pathways), i.e., within a treatment strategy consistent with current consensus guidelines whereby selexipag is the only IP-receptor agonist given a Class I evidence recommendation for sequential drug combination therapy [Galiè 2015].

Pediatric PAH is a rare and progressive disorder associated with considerable morbidity and mortality. Current treatment recommendations in the pediatric population include PDE-5 inhibitors, ERAs, and inhaled, subcutaneous, and i.v. prostacyclin-pathway agonists [Ivy 2013, Galiè 2015]. However, in the absence of randomized controlled clinical trials powered to show the efficacy of those therapies in pediatric patients, the treatment algorithm is based on evidence from adult studies.

Further clinical trials in the pediatric population are therefore extremely important to provide more data for the management of PAH in children.

Given the pathophysiological and clinical similarities of pediatric and adult PAH disease, it is believed that pediatric participants with PAH could benefit from selexipag treatment. This study aims to determine the appropriate dose and to investigate the PK, safety, and tolerability of selexipag in pediatric participants over 2 years of age with PAH.

1.4.2 Risks

The tolerability and safety profile of selexipag administered to children is expected to be consistent with that of adult patients [see Section 1.2.3.4].

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

- The selection of the starting dose for pediatric participants is based on their body weight category, using the data from the population PK model in the GRIPHON study, targeting the exposure observed in adult participants with PAH at a starting dose of 200 µg.
- At the interim and final PK analyses, all available PK results will be used to update the PK model and to confirm or adjust the dose selection.
- Enrollment of Cohort 3 (children aged from 2 to less than 6 years old) will only be performed after the PK interim analysis in Cohorts 1 and 2 (pediatric participants older than 6 years) have been completed, and selexipag safety and tolerability profiles in Cohorts 1 and 2 have been confirmed.
- The number of PK samples and blood volume collected per participant will be optimized to reduce the total amount of blood drawn from pediatric participants [see Section 7.2.5.1].
- Inclusion and exclusion criteria are carefully designed in this protocol [see Section 4].
- Close monitoring during the initial up-titration period up to Week 12 includes weekly phone calls or site visits, followed by 3-monthly contacts (phone calls and site visits alternating every 3 months) [see Figure 2, Table 4, and Table 5].
- Specific recommendations are made regarding the management of AEs associated with tolerability during the initial up-titration phase [see Section 5.1.4], along with the recommendation that participants take study drug with food to improve tolerability [see Section 5.1.4].
- Specific recommendations are made for study drug interruption and/or permanent discontinuation [see Section 5.1.10].
- Guidance to investigator and parents/participants in case of clinical signs compatible with gastrointestinal ileus or obstruction [see Sections 1.2.2 and 5.1.10].
- Guidance to investigator and parents/participants in case of clinical signs of hyperthyroidism [see Sections 1.2.3.4 and 5.1.10].
- Monitoring of participants' growth and development throughout their study participation [see Sections 7.2.3.4. and 7.2.3.5].

Safety surveillance for participants participating in study AC-065A203 will additionally be ensured by an Independent Data Safety Monitoring Committee (IDMC), which will periodically review available safety data [see Section 3.3].

Participants will receive additional care as result of being in a clinical trial including close monitoring at an expert PAH center.

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

1.4.3 Conclusion

The benefit of medicines acting on the prostacyclin pathway (IP-receptor agonists) in the treatment of PAH in adults is established, as acknowledged by current treatment guidelines [Galiè 2015].

Uptravi (selexipag) is a selective IP-receptor agonist for oral use with proven efficacy and safety in adults with PAH. To date, selexipag is the only IP-receptor agonist approved globally for long-term treatment across WHO FC II III, and primarily in combination with current first-line oral PAH-specific medicines, in adult patients in need of additional therapy because of insufficient disease control. Uptravi represents an important additional treatment option for these patients.

Selexipag is not indicated or foreseen for use as an alternative to i.v. prostacyclin analogs (epoprostenol, treprostinil) in patients with the most severe PAH (WHO FC IV).

The availability of selexipag, a highly selective IP-receptor agonist for oral use and with demonstrated benefit for PAH disease outcomes in add-on therapy, provides an important rationale for initiating prostacyclin-pathway therapy at a medically appropriate stage of PAH disease without major consequences for the patient's lifestyle.

Based on the known similarities between PAH disease in adult and pediatric patients and the need to develop treatments that may be disease-modifying in pediatric patients with PAH, this study is the first clinical study conducted with selexipag in children with PAH.

2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective of the study is to confirm the selexipag starting dose(s), selected based on PK extrapolation from adults, that leads to similar exposure as adults doses in children from ≥ 2 to < 18 years of age with PAH, by investigating the PK of selexipag and its active metabolite ACT-333679 in this population.

2.2 Secondary objectives

- To evaluate the safety and tolerability of selexipag in children from ≥ 2 to < 18 years of age with PAH.

2.3 Exploratory objectives

- To explore the relationship between drug exposure at the iMTD and 6MWD at each time point of assessment.
- To explore the relationship between drug exposure and NT pro-BNP at each time point of assessment.
- To explore the relationship between drug exposure and Echo variables at each time point of assessment.
- To explore the time to disease progression / clinical worsening from first study drug dose up to EOT + 7 days.

2.4 Other objectives

- To assess the palatability of selexipag formulation at each time point of assessment using a 5-point facial hedonic scale.
- To assess the acceptability of selexipag formulation at each time point of assessment using a 3-point categorical scale.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, open-label, single-arm Phase 2 study.

Approximately 60 participants will be enrolled in 3 different age cohorts (based on age at Baseline / Enrollment / Visit 2) to obtain at least 45 participants with evaluable PK profiles:

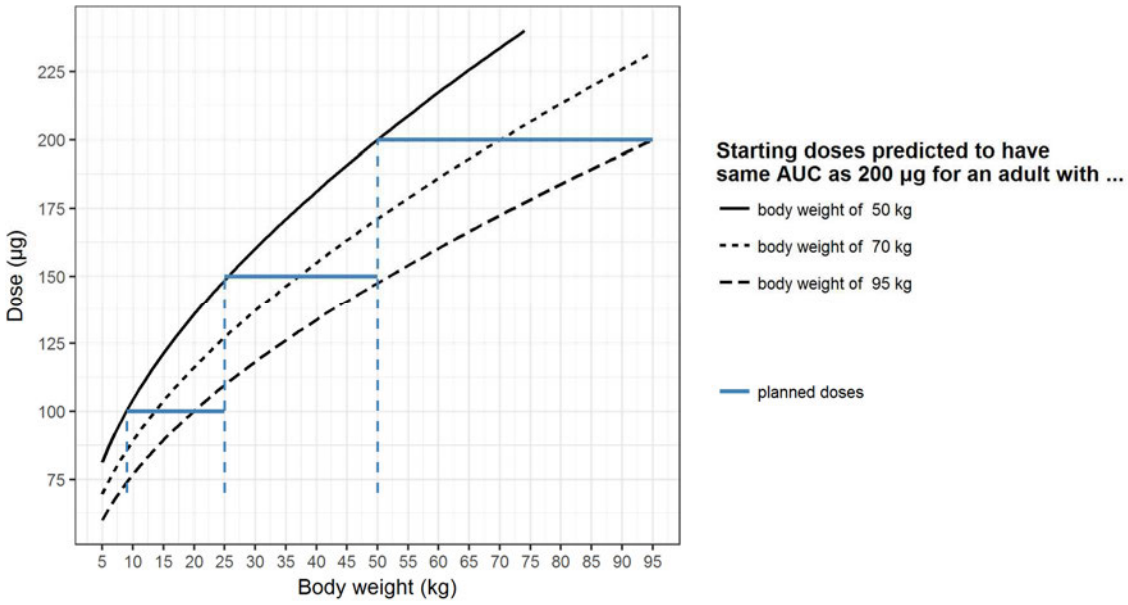
- Cohort 1: ≥ 12 to < 18 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles)
- Cohort 2: ≥ 6 to < 12 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles)
- Cohort 3: ≥ 2 to < 6 years of age (approximately 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles).

The starting dose is based on the body weight category of the participants, using the data from the population PK model in the GRIPHON/AC-065A302 study targeting the exposure observed in adult participants with PAH at a starting dose of 200 µg [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014]. The continuous relationship between dose and body weight is used to define body weight categories and starting dose for each body weight category such that on average the exposure (combined exposure over one dosing interval at steady state [$AUC_{\tau,ss,combined}$]) will be comparable to that in a 70 kg adult but not exceeding the exposure in a 50 kg adult [Figure 1, Modeling and Simulation Report, Pediatric dose selection 2016]:

- 100 µg for participants with a body weight from ≥ 9 to < 25 kg.
- 150 µg for participants with a body weight from ≥ 25 to < 50 kg.
- 200 µg for participants with a body weight ≥ 50 kg.

The body weight-exposure relationship is extrapolated from the body weight-exposure relationship determined by the population PK model in participants with PAH in the GRIPHON study with body weights ranging from 40 148 kg. In this model, body weight was a covariate on selexipag and ACT-333679 volume of distribution and elimination rate [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014].

Figure 1 **Estimated starting doses based on the GRIPHON PK model achieving the same exposure as in adult patients of 50 kg, 70 kg, and 96 kg treated with 200 µg b.i.d. selexipag**



AUC area under the curve; b.i.d. twice daily; GRIPHON prostacyclin (PG12G) receptor agonist in pulmonary arterial hypertension; PK pharmacokinetic.

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

$AUC_{\tau,ss,combined}$ $1/38 \times AUC_{\tau,ss,\ selexipag} + 37/38 \times AUC_{\tau,ss\ ACT\ 333679}$

The potency of ACT-333679 was estimated to be 37 times that of selexipag. ACT-333679 is, therefore, the major contributor to the efficacy of selexipag [Menyhart 2014]. The starting dose selection will be confirmed or adjusted after the completion of each age cohort by updating the population PK model (interim analysis).

The study will be conducted in approximately 30 sites in 20 countries.

Enrollment will start with both Cohort 1 and Cohort 2 (participants ≥ 12 to < 18 and ≥ 6 to < 12 years old, respectively). After completion of PK assessments in at least 15 participants from Cohort 1 at Week 12, the dose-exposure relationship will be established using a population PK model [Modeling and Simulation Report, Pediatric dose selection 2016]. The PK data from any participants in Cohort 2 who have completed their PK assessments at this time will be included in this first interim analysis.

Results of this model-based analysis will be used to confirm or adjust the selexipag doses initially selected. If the population PK model results suggest that the administered selexipag doses lead to exposures deviating from the currently predicted target exposures, the recommended starting dose, increments of up-titration, and maximum allowed dose (equivalent to 1,600 µg b.i.d. in adult participants with PAH) for the remaining participants to be enrolled in Cohort 2 and Cohort 3 will be adjusted. The decision on dose-adjustment will take into account the inter-individual variability in the pediatric population and the difference in exposure between lower and upper limits of body weight in the GRIPHON study. The inter-individual variability in the GRIPHON study was more than 30% (comparing the 10^{th} and 90^{th} percentiles), and difference in exposure between lower and upper limits of body weight was 50% [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014]. It is expected that the dosing regimen does not need to be adjusted if the revised point estimate body weight-starting dose relationship deviates from the current estimate by less than 30%. The dosing regimen must be adjusted if the revised point estimate body weight-starting dose relationship deviates from the current estimate by more than 50%. If this difference between the revised and the current point estimate is between 30% and 50%, the decision on dose adjustment will depend on the results of safety assessments after the first dose. Enrollment of Cohort 3 (children ≥ 2 to < 6 years of age) will start once the appropriate doses have been confirmed by modelling and simulation in a second interim analysis of PK data from the children older than 6 years (i.e., Cohorts 1 and 2), and if there is no safety concern based on IDMC reviews.

The PK data pooled from all three age cohorts will be modelled to allow dosing recommendations for all children ≥ 2 years of age. A final PK analysis will be prepared based on the overall PK and safety data up to Week 16 evaluation.

Given the rareness of pediatric PAH, combined with the ongoing global Corona virus disease-2019 (COVID-19) pandemic, enrolling participants in age Cohort 3 (≥ 2 to < 6 years of age) into this study has been difficult and as such the planned sample size of at least 15 PK evaluable Cohort 3 participants remains a challenge. The option of confirming the selexipag dosing recommendation for participants aged ≥ 2 to < 6 years based on a smaller sample size is, therefore, being considered. To assess this, a third interim PK analysis may be conducted, as deemed appropriate by the sponsor.

All available PK and safety data from participants in Cohorts 1, 2, and 3 up to Week 16 at the time of the data cut-off date, will be included in interim analysis 3. The analytical approach for interim analysis 3 will be the same as applied for interim analyses 1 and 2. For the dosing confirmation of Cohort 3 with fewer than the planned 15 PK evaluable participants, one of the following criteria is to be achieved:

- The 90% CI of the point estimate describing the body weight-starting dose relationship relative to the current estimate is within 0.70-1.30.

Or

- The 90% CI of the point estimate describing the body weight-starting dose relationship relative to the current estimate is within 0.50-1.50 and at the same time, no dose adjustment is warranted by the available safety data.

If, however, the 90% CI of the relative point estimate exceeds 0.70-1.30 and a dose adjustment may be warranted by the available safety data or the 90% CI of the relative point estimate exceeds 0.50-1.50, a final PK analysis including the PK data pooled from all 3 age cohorts and at least 15 PK available participants in Cohort 3, will be conducted. Following this final PK analysis, the dosing recommendation will be confirmed based on the revised point estimate body weight-starting dose relationship, irrespective of the 90% CI, as originally planned.

In case the dosing recommendation for age Cohort 3 is confirmed based on the third interim PK analysis, further enrolment into the trial will be terminated. The PK of all enrolled participants, including participants completing their PK assessments after the data cut-off date for interim analysis 3 will be included in the PK analysis to be reported in the clinical study report (CSR).

The selection of the dosing regimen for the Phase 3 study will be based on the safety, tolerability, and PK results evaluated in the interim or final PK analysis (as applicable).

Participants who discontinue the treatment any time before the profile PK sampling day may be replaced within the age cohort.

3.1.1 Study periods

The study consists of the following consecutive periods:

Screening period: Lasts up to 42 days; starts with the signature of the informed consent form (ICF) and ends with the administration of the first study treatment dose.

Treatment period: Starts from the first dose of study treatment at Baseline/Enrollment visit and ends on the day of the last dose of selexipag (EOT). This includes:

- **Up-titration period:**

  From the first dose of study treatment until the participant reaches their iMTD. This period is estimated to last up to 12 weeks.

  Details of up-titration are described in Section 5.1.4.

- **Maintenance period:**

  After Week 12: The participants will continue study treatment at the same dose up to Week 16.

After Week 16: Study treatment will continue as long as it remains beneficial for the participant, but up to a maximum of 5 years after last participant first visit [see Section 3.1.2 for details].

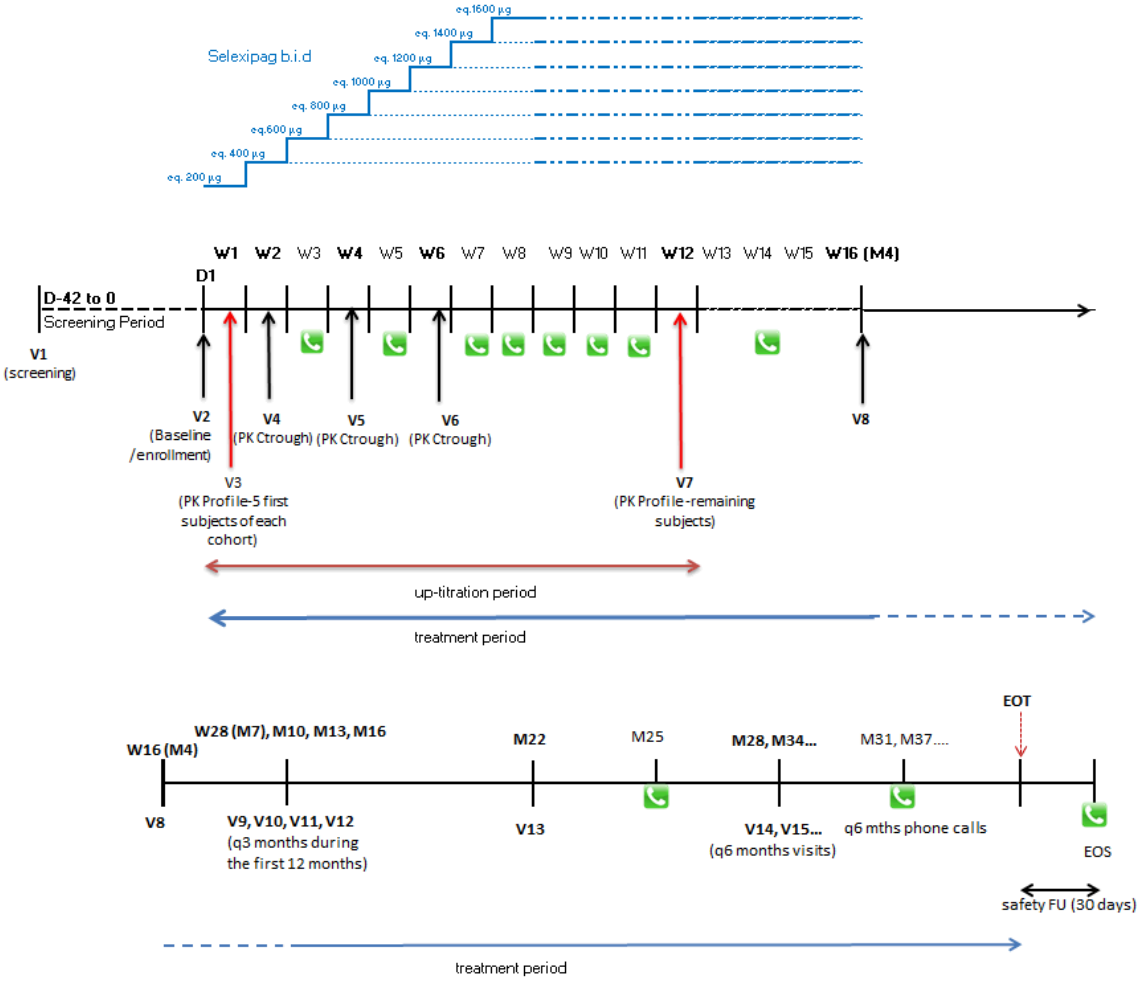
EOT visit: This visit should be conducted within 1 week of the last dose of study treatment.

Safety Follow-up period: Starts on the day after the last dose of study treatment and ends about 30 days thereafter with a phone call that will serve as the End-of-Study (EOS).

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

The overall study design is depicted in Figure 2.

Figure 2 Study design



b.i.d twice daily; D day; eq. equivalent; EOS End of Study; EOT End of Treatment; FU follow up; M month; q every; V visit; W week.
Equivalent (eq.) refers to the equivalent dose according to the body weight category as described in Section 5.1.4.

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., first ICF signed) and ends with the last visit of the last participant (i.e., last EOS).

The study will last until 5 years after last participant, first visit.

Participants will be treated with selexipag as long as the treatment is beneficial to the participant, per the investigator's decision. After the last dose of selexipag, participants will be followed up for safety until 30 days after the last dose (EOS visit). The participant's participation is completed with the EOS visit.

3.2 Study design rationale

The objective of this pediatric study is to confirm the selexipag starting doses, selected by PK extrapolation from adults, that are expected to lead to similar exposure of selexipag and its active metabolite ACT-333679 in children as in adult PAH subjects(GRIPHON), following the same principle of up-titration to the iMTD. The primary PK endpoint is defined as exposure ($AUC_{\tau,ss,combined}$) to selexipag and ACT-333679 corrected for potency, determined during the 12-week up-titration period. The PK parameters will be described with a population PK model and will be used to confirm/adjust the selected selexipag doses [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014, Modeling and Simulation Report, Pediatric dose selection 2016]. The $AUC_{\tau,ss,combined}$ in adult participants with PAH was also determined based on population PK modeling [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014].

The following assumptions were used for the calculation of the starting dose in pediatric participants with PAH based on the GRIPHON model.

- In adults, the PK of selexipag and the active metabolite ACT-333679, after multiple-dose administration, are dose-proportional up to 1,800 µg, given b.i.d. [Clinical Study Report AC-065A-101 2012, QGUY/2006/NS304/-01].
- It is assumed that the PK are also dose proportional in the pediatric population, and this will be further evaluated in the proposed study.
- The enzyme systems involved in selexipag metabolism (CES1, CES2, CYP2C8, UGT1A3, and UGT2B7), and CYP3A4, are essentially mature in children aged 2 years and older [Song 2017, Hines 2016, Smits 2012, McNamara 2002, Zhu 2009, Shi 2011, Yang 2009, Strassburg 2002, Oo 2003].
- No other major differences between the PK of selexipag in adults and children are expected.

The PK of selexipag and its active metabolite ACT-333679 in adult PAH subjects were characterized by a population PK model based on data from the GRIPHON study

[Modeling and Simulation Report AC-065A302 (GRIPHON) 2014]. Body weight was identified as a statistically significant covariate for the volume of distribution of selexipag and ACT-333679, as well as for drug clearance. The model-predicted concentrations of selexipag and ACT-333679 for a reference subject of 70 kg were compared to model-predicted concentrations for subjects with body weights of 51 and 96 kg, corresponding to the 10th and 90th percentile of the body weight distribution of subjects included in the GRIPHON study, at steady-state doses of 1,600 µg b.i.d.

Compared to a 70 kg subject, a subject with a body weight of 51 kg is predicted to have 30% and 20% higher exposure to selexipag and to ACT-333679, respectively, whereas a subject with a body weight of 96 kg is predicted to have 20% and 10% lower exposure, respectively.

The selection of the starting dose for pediatric participants is based on body weight categories, using the data from the population PK model in the GRIPHON study, targeting the exposure observed in adult participants with PAH at a starting dose of 200 µg [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014]. The exposure is defined as the combined exposure to selexipag and ACT-333679 corrected for potency ($AUC_{\tau,ss,combined}$). The potency of ACT-333679 was estimated to be 37 times that of selexipag. ACT-333679 is, therefore, the major contributor to the efficacy of selexipag.

The continuous relationship between dose and body weight is used to define body weight categories and starting dose for each body weight category such that on average the exposure ($AUC_{\tau,ss,combined}$) will be comparable to that in a 70 kg adult patient but not exceeding the exposure in a 50 kg adult patient [Figure 1].

The starting dose of selexipag expressed on a per kg basis increases in the lower body weight categories, as the relationship between body weight and dose is not linear. This is analogous with the pediatric experience with epoprostenol, where the doses in pediatric patients are generally higher than in adults on a per kg basis. However, assuming the body weight-to-exposure relationship observed in GRIPHON, $AUC_{\tau,ss,combined}$ at the starting dose for pediatric patients in different body weight categories will not be higher than $AUC_{\tau,ss,combined}$ at a starting dose of 200 µg b.i.d. in a 50 kg adult patient in the GRIPHON study.

In adult PAH patients, the recommended starting dose of 200 µg b.i.d. is up-titrated in increments of 200 µg b.i.d. at approximately weekly intervals up to the iMTD or 1,600 µg b.i.d. [Clinical Study Report AC-065A302 (GRIPHON) 2014]. Individual up-titration in children will be similar to that in adult PAH patients, i.e., the dose will be increased by increments equal to the starting dose up to the iMTD and will not exceed the dose with predicted equivalent exposure to 1,600 µg b.i.d. in each body weight category. Based on

the dose-proportional PK of selexipag/ACT-333679, the ratio of the maximum pediatric dose to the adult dose for each dose level is the same as for the starting dose.

The identification of starting doses, the increment to be applied to children treated with selexipag according to their body weight category, and the maximum allowed dose in this study will serve as a basis for the Phase 3 trial design.

3.3 Study committees

An IDMC has the overall responsibility for safeguarding the interests of participants by monitoring safety data obtained in the study and by making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The PK results of the interim analyses (after completion of Cohort 1 and 2), and overall PK results of all three cohorts will be provided to the IDMC for review, if requested by the committee. The IDMC will be fully operational prior to the enrollment of the first participant in the study. The composition and operation of the IDMC is described in the IDMC charter.

4 SUBJECT POPULATION

4.1 Subject population description

Participants with iPAH or hPAH, as well as aPAH-CHD, drug or toxin-induced PAH, PAH-aCTD, or PAH associated with HIV are enrolled if they are of WHO FC II or III. Eligible participants are participants treated with an ERA and/or a PDE-5 inhibitor or participants who are not candidates for these therapies.

Participants will be enrolled in age cohorts, starting with participants from 6 to less than 18 years of age.

The population is vulnerable according to the ICH-GCP E6 1.61 definition. Parent(s) / legally authorized representative(s) (LAR[s]) will be required to provide informed consent for the participation of their child in the clinical study, and assent will be obtained from developmentally capable study participants.

4.2 Rationale for the selection of the study population

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

Participants under 2 years of age are not part of the study population due to concerns of a potentially increased risk of intestinal intussusception, based on toxicological findings of intestinal intussusception in young dogs treated with selexipag and the high background

incidence of intussusception in infants [Newman 1987, Hutchison 1980, Pollack 1991, Waseem 2008, Stringer 1992].

4.3 Inclusion criteria

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

1. Signed and dated informed consent by the parent(s) or LAR(s) AND assent from developmentally capable children.
2. Males or females between ≥ 2 and < 18 years of age at Baseline / Enrollment / Visit 2 weighing ≥ 9 kg.
3. PAH diagnosis confirmed by documented historical RHC performed at any time before the participant's enrollment, and characterized by:
   - mPAP ≥ 25 mmHg;

   and
   - PAWP ≤ 15 mmHg

     (in the absence of pulmonary vein obstruction and/or significant lung disease, PAWP can be replaced by LAP or, in the absence of mitral stenosis, by LVEDP);

   and
   - PVRi > 3 WU × m^2.
4. PAH belonging to Nice 2013 Updated Classification Group 1 (including Down syndrome) and of one of the following etiologies:
   - iPAH.
   - hPAH.
   - aPAH-CHD:

     PAH with co-incidental CHD.

     Post-operative PAH (persisting / recurring / developing ≥ 6 months after repair of CHD).
   - Drug or toxin-induced PAH.
   - PAH associated with HIV.
   - PAH-aCTD.
5. WHO FC II to III.
6. Subjects treated with an ERA and/or a PDE-5 inhibitor, provided that the treatment dose(s) has been stable for at least 3 months prior to enrollment, or participants who are not candidates for these therapies.

7. Females of childbearing potential must have a negative pregnancy test at Screening and at Enrollment, and must agree to undertake monthly pregnancy tests and to use a reliable method of contraception (if sexually active) from Screening up to study drug discontinuation + 30 days (EOS).

4.4 Exclusion criteria

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

Etiology

1. Participants with PAH due to portal hypertension, schistosomiasis, PVOD, and/or pulmonary capillary hemangiomatosis.
2. Participants with PAH associated with Eisenmenger syndrome.
3. Participants with moderate to large left-to-right shunts[5].
4. Participants with cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, univentricular heart, or pulmonary atresia with ventricular septal defect, as well as participants with Fontan palliation.
5. Participants with PH due to lung disease and/or hypoxia. For participants with Down syndrome, exclusion of lung disease and hypoxia causing PH should be documented (eg, computed tomography scan, polysomnography, lung function tests).

Treatment and intervention

6. Previous treatment with Uptravi (selexipag) within 2 weeks prior to enrollment.
7. Participants who have received prostacyclin (epoprostenol) or prostacyclin analogs[6] (i.e., treprostinil, iloprost, beraprost) within 2 months prior to enrollment or who are scheduled to receive any of these compounds during the trial.
8. Treatment with another investigational drug within 4 weeks prior to enrollment.
9. Treatment with strong and moderate inhibitors of CYP2C8 (eg, gemfibrozil, clopidogrel, deferasirox, teriflunomide) within 2 weeks prior to enrollment until the last dose of selexipag + 3 days.

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

[6] Single administration of drugs used for acute vasodilator testing during RHC procedure is allowed (eg, i.v./inhaled prostacyclin, inhaled nitric oxide, or oral sildenafil).

10. Treatment with inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole) is prohibited from 2 weeks prior to enrollment and until the last dose of selexipag + 3 days.
11. Any PAH-related surgical intervention planned, or participants listed for organ transplantation related to PAH.
12. History or current suspicion of intussusception or ileus or gastrointestinal obstruction, per investigator's judgment.

Baseline abnormalities

13. Known concomitant life-threatening disease with a life expectancy < 12 months.
14. Uncontrolled thyroid disease, per investigator's judgment.
15. Hemoglobin or hematocrit < 75% of the lower limit of normal range.
16. 1[7]. Moderate or severe hepatic impairment, eg, Child-Pugh Class B or C[8].
17. Clinical signs of hypotension that in the investigator's judgment would preclude initiation of a PAH-specific therapy.
18. Participants with severe renal insufficiency (estimated creatinine clearance < 30 mL/min or serum creatinine > 221 µmol/L).
19. Severe coronary heart disease or unstable angina as assessed by the investigator.
20. Myocardial infarction within the last 6 months prior to enrollment.
21. Decompensated cardiac failure if not under close supervision.
22. Severe arrhythmias as assessed by the investigator.
23. Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months prior to enrollment.
24. Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH.

Pregnancy and breastfeeding

25. Pregnancy (including family planning) or breastfeeding.

[7] Sub numbering introduced to highlight change from previous protocol version.

[8] The assessment for hepatic impairment at Screening (Child Pugh Score, see Section 14.4 Appendix 4) must be fully documented for participants with hepatic impairment as part of medical history and clinical signs and evidence (from central and/or local lab) of hepatic impairment.

Other categories

26. Known hypersensitivity to the investigational treatment or to any of the excipients of the drug formulations.
27. Drug or substance abuse, or any condition that, in the opinion of the investigator, may prevent compliance with the protocol or adherence to study treatment.
28. Loss of 250 mL or more of blood within 3 months prior to Screening.
29. History or clinical evidence of any disease and/or existence of any surgical or medical condition that might interfere with the absorption, distribution, metabolism, or excretion of the study treatment(s) (eg, cholecystectomy).
30. " Criterion deleted per Amendment 6."

4.5 Criteria for female subjects of childbearing potential

Pregnancy is associated with maternal mortality in participants with PAH [Bédard 2009]. Therefore, female participants of childbearing potential who are heterosexually active must use a reliable method of contraception.

4.5.1 Definition of childbearing potential

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

- Prepubescence
- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy, or hysterectomy
- Tubal sterilization
- Premature ovarian failure confirmed by a specialist
- XY genotype or any other genetic disorder associated with permanent sterility, uterine agenesis

In the case of prepubescence, potential childbearing status will be assessed at each visit and recorded in the electronic case report form (eCRF). The reason for not being considered to be of childbearing potential will be recorded in the eCRF.

4.5.2 Acceptable methods of contraception

For female participants who are of childbearing potential [see definition in Section 4.5.1] and heterosexually active, it is mandatory to use one of the following methods of birth control from Screening up to at least 30 days after study treatment discontinuation.

- Oral or injectable contraceptive agents, implants or transdermal contraceptive hormone

- Intrauterine device
- Vasectomized partner (a vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used).
- Diaphragm; female condom or cervical cap; or partner's use of a condom, and any of these used in combination with a spermicide.

If a hormonal contraceptive is chosen, it must be taken for at least 30 days prior to randomization.

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

It is the responsibility of the investigator to ensure appropriate counseling, including consultation with a specialist (if needed), to the participant and/or parent(s)/LAR(s) on the acceptable method of contraception.

In female participants of childbearing potential who become heterosexually active at any time after enrollment, contraceptive method(s) that are immediately effective must be initiated. This method(s) can be replaced but must continue until the new method of contraception becomes effective. The contraceptive methods used (including non-pharmacological methods) must be recorded in the eCRF.

If the female participant or her parent(s)/LAR(s) decide that they want to change the form of birth control used, they need to talk with the treating physician to be sure that another acceptable form of birth control is chosen.

To ensure compliance, the study personnel must remind female participants of childbearing potential who are heterosexually active and their parent(s)/LAR(s) at each visit to use the methods of contraception defined for this study. These reminders must be documented in the source documents.

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment: description and rationale

Selexipag is supplied by the sponsor as child-proof bottles containing tablets with the following dosage strengths:

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

5.1.2 Study treatment administration

Selexipag is administered orally b.i.d. with an interval of approximately 12 hours.

Tablets can be administered via 1 of 3 options:

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

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

Administration of tablets with soft-food

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

a) .Take the instructed number of tablets (200 µg tablets and/or 50 µg mini-tablets) as shown in the respective protocol uptitration scheme.

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

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

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

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

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

Administration of mini-tablets with juices

The 50 µg mini-tablets can also be administered by dispersing in apple- or orange-juice:

a) Place the instructed number of mini-tablets as shown in uptitration scheme in a beverage recipient made of glass or porcelain. The minimal volume of beverage to disperse the mini-tablet, must be 1 mL per mini-tablet.

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

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

As the study drug starting dose is based on body weight, calibration certificates or maintenance records for the body weight scale should be available prior to the first participant being enrolled at the site. The calibration should be performed according to the manufacturer's specification.

At the beginning of each up-titration phase, participants will be recommended to take the first dose in the evening in order to reduce the likelihood of the occurrence of headache, jaw pain, flushing, and nausea. The study drug can be taken with or without food (ie a meal), although tolerability may improve when selexipag is taken with food.

On visits when PK samples are scheduled (Visit 3 or 7; Visits 4, 5, and 6), the selexipag dose must be taken at the site under investigator / site staff supervision to ensure exact recording of dose intake time and compliance with the blood samples time schedule:

- Visit 3 or 7 (PK sampling over 12 h): the morning and evening doses should be taken at the site:

  The morning dose after pre-dose PK sample.

  The evening dose after the 12 hours post-dose PK sample.
- Visits 4, 5, and 6:

  The morning dose should be taken at the site after the trough PK sample.

The investigator / site staff must ensure that all PK samples are collected after 3 days at the same dose and using the same mode of treatment administration. Exact date and time of the treatment intakes preceding and following all PK samples, as well as the mode of treatment administration, must be recorded in the source documents and the eCRF.

See also instructions regarding meals on the PK visit days in Section 7.2.5.2.

5.1.3 Treatment assignment

After having verified that the participant meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the Interactive Response Technology (IRT) system at the Baseline/Enrollment visit to enroll the participant. The IRT assigns an enrollment number to the participant and assigns the treatment bottle numbers, based on the participant's body weight category.

5.1.4 Study drug starting dose and up-titration

At the Baseline/Enrollment visit, based on the participant's body weight, the body weight category, starting dose, and up-titration scheme will be determined.

Study medication administration will start in the evening of Day 1 and continue thereafter with b.i.d. dosing, i.e., in the morning and in the evening. During the up-titration period of 12 weeks, it is recommended that the doses are increased weekly in increments equal to the starting dose until the participants reach their iMTD or until a maximum dose corresponding to their baseline body weight category is achieved.

To improve tolerability, it is recommended that the study drug, selexipag, is taken with food and, at the beginning of each up-titration phase, that the first increased dose is taken in the evening. The maximum dose allowed to be administered will be 8-fold the corresponding starting dose:

- Body weight category ≥ 50 kg: starting dose of 200 µg titrated up to the iMTD of 1,600 µg b.i.d. Participants in this category will receive 200 µg tablets only [Table 1].
- Body weight category ≥ 25 to < 50 kg: starting dose of 150 µg titrated up to the iMTD of 1,200 µg b.i.d. Participants in this category will receive a combination of 50 µg mini-tablets and 200 µg tablets [Table 2].
- Body weight category ≥ 9 to < 25 kg: starting dose of 100 µg titrated up to the iMTD of 800 µg b.i.d. Participants in this category will receive either a combination of 50 µg mini-tablets and 200 µg tablets, or 50 µg mini-tablets only, if requested by the investigator [Table 3].

  Two study-treatment supply options are available:

  Option 1 will supply participants able to swallow tablets whole with water with a combination of 200 µg tablets and 50 µg mini-tablets to minimize the overall number of tablets per intake and will be provided via IRT by default, and

  Option 2 will supply participants with 50 µg mini-tablets only upon request by investigator, if study treatment is to be taken with soft food or dispersed in apple/ orange juice.

The up-titration will be agreed upon during scheduled telephone calls or visits.

At Week 12 the iMTD for each participant will be determined. This dose should be kept unchanged until Week 16.

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

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

If a participant has tolerability issues and experiences adverse reactions reflecting the mode of action for selexipag [see Section 5.1.10], the dose can remain the same without further up-titration (pause in up-titration). Up-titration can be resumed after the pause, or the dose can be reduced to the previous dose level. The decision to pause up-titration, to up-titrate or down-titrate study drug, or to permanently discontinue study drug treatment will be based on the investigator's medical judgment [see Section 5.1.10].

If a dose of selexipag is missed, participants should take a dose as soon as possible unless the next dose is within the next 6 h. During the up-titration period, the investigator / site staff must ensure that PK samples are collected after 3 days at the same dose and using the same mode of administration.

At any time during study treatment, study drug interruptions (eg, missed doses for any reason) of 3 days or more will require a new up-titration according to the scheme from Day 1.

All selexipag dose changes and reasons for dose interruptions must be documented in the eCRF.

Table 1 Up-titration dosing scheme for body weight category ≥ 50 kg

Period	**Duration**	**Dose regimen**	**Number of 200 µg tablets (b.i.d.)**	**Number of 50 µg mini-tablets (b.i.d.)**
First dose	Day 1 p.m.	200 µg	1	-
Up-titration	Day 2 a.m. to Day 8 a.m.	200 µg b.i.d.	1	-
	Day 8 p.m. to Day 15 a.m.	400 µg b.i.d.*	2	-
	Day 15 p.m. to Day 22 a.m.	600 µg b.i.d.*	3	-
	Day 22 p.m. to Week 4 a.m.	800 µg b.i.d.*	4	-
	Week 4 p.m. to Week 5 a.m.	1000 µg b.i.d.*	5	-
	Week 5 p.m. to Week 6 a.m.	1200 µg b.i.d.*	6	-
	Week 6 p.m. to Week 7 a.m.	1400 µg b.i.d.*	7	-
	Week 7 p.m. to Week 8 a.m.	1600 µg b.i.d.*	8	-
Maintenance	From Week 12 throughout the study	iMTD: 200 1600 µg b.i.d.	1 8	-

b.i.d. twice daily; iMTD individual maximum tolerated dose.
* Or the highest tolerated dose until Week 12.

Table 2 Up-titration dosing scheme for body weight category ≥ 25 to < 50 kg

Period	**Duration**	**Dose regimen**	**Number of 200 µg tablets (b.i.d.)**	**Number of 50 µg mini-tablets (b.i.d.)**
First dose	Day 1 p.m.	150 µg	-	3
Up-titration	Day 2 a.m. to Day 8 a.m.	150 µg b.i.d.	-	3
	Day 8 p.m. to Day 15 a.m.	300 µg b.i.d.*	1	2
	Day 15 p.m. to Day 22 a.m.	450 µg b.i.d.*	2	1
	Day 22 p.m. to Week 4 a.m.	600 µg b.i.d.*	3	-
	Week 4 p.m. to Week 5 a.m.	750 µg b.i.d.*	3	3
	Week 5 p.m. to Week 6 a.m.	900 µg b.i.d.*	4	2
	Week 6 p.m. to Week 7 a.m.	1050 µg b.i.d.*	5	1
	Week 7 p.m. to Week 8 a.m.	1200 µg b.i.d.*	6	-
Maintenance	From Week 12 throughout the study	iMTD: 150 1200 µg b.i.d.	1 6	0 3

b.i.d. twice daily; iMTD individual maximum tolerated dose.
* Or the highest tolerated dose until Week 12.

Table 3 Up-titration dosing scheme for body weight category ≥ 9 to < 25 kg

			Option 1		**Option 2**
Period	**Duration**	**Dose regimen**	**Number of 200 µg tablets (b.i.d.)**	**Number of 50 µg mini-tablets (b.i.d.)**	**Number of 50 µg mini-tablets (b.i.d.)**
First dose	Day 1 in the evening (p.m.)	100 µg	-	2	2
Up-titration	Day 2 a.m. to Day 8 a.m.	100 µg b.i.d.	-	2	2
	Day 8 p.m. to Day 15 a.m.	200 µg b.i.d.*	1	-	4
	Day 15 p.m. to Day 22 a.m.	300 µg b.i.d.*	1	2	6
	Day 22 p.m. to Week 4 a.m.	400 µg b.i.d.*	2	-	8
	Week 4 p.m. to Week 5 a.m.	500 µg b.i.d.*	2	2	10
	Week 5 p.m. to Week 6 a.m.	600 µg b.i.d.*	3	-	12
	Week 6 p.m. to Week 7 a.m.	700 µg b.i.d.*	3	2	14
	Week 7 p.m. to Week 8 a.m.	800 µg b.i.d.*	4	-	16
Maintenance	From Week 12 throughout the study	iMTD: 100 800 µg b.i.d.	1 4	0 or 2	2 16

b.i.d. twice daily; iMTD individual maximum tolerated dose.
* Or the highest tolerated dose until Week 12.

5.1.5 Blinding

Not applicable.

5.1.6 Study treatment supply

Selexipag 200 µg tablets and 50 µg mini-tablets are supplied by the Sponsor.

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

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

5.1.6.1 Study treatment packaging and labeling

Study treatment is provided as tablets and supplied in childproof bottles:

- Selexipag 200 µg: bottles of 120 tablets.
- Selexipag 50 µg: bottles of 280 mini-tablets.

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

5.1.6.2 Study treatment distribution and storage

The sponsor will supply all study drug(s) to the site according to local regulations.

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

The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study.

5.1.6.3 Study treatment dispensing

At each dispensation visit, the IRT will be used to assign study treatment bottles.

The participants will receive sufficient study treatment to cover the period until the next treatment dispensation visit.

Participants are asked to return all used, partially used, and unused study treatment bottles at each treatment dispensation visit from Visit 2. The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the Sponsor. The IRT will allow dispensation of study drug outside of the scheduled visits. An accurate record of the date and amount of study treatment dispensed to each participant must be available for inspection at any time.

5.1.6.4 Study treatment return and destruction

The protocol-mandated study treatment return procedures may not be altered without prior written approval from the Sponsor. On an ongoing basis and/or on termination of the study, the clinical research associate (CRA) will collect used and unused treatment kits, which will be sent to the warehouse where the Sponsor personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by the Sponsor personnel or the deputy and written permission for destruction has been obtained from the Sponsor.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 Study treatment accountability

The inventory of study treatment dispensed to and returned by the participant's parent(s)/LAR(s) (i.e., study-treatment accountability) must be performed by site personnel at visits, indicated in the assessment schedule [Table 4 and Table 5], when the investigational medicinal product is to be brought back to the site and before dispensing further study treatment. It is to be recorded by site personnel on the study treatment dispensing and accountability log and in the eCRF, and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (i.e., bottle) dispensed to the participant:

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

Site staff will ensure study drug is accounted for by trained personnel under controlled conditions following the study instructions.

At the dispensing visits and at the EOT visit, all study treatment supplies, including partially used and/or empty bottles, must be returned and retained at the site for review by the CRA during the monitoring visits.

If the participant's parent(s)/LAR(s) forgets to bring the remaining study treatment to a study dispensing or EOT visit, they must be instructed not to provide the participant with any tablets from the remaining study treatment bottles and to return them at the next visit.

5.1.7.2 Study treatment compliance

A Study Drug Diary is provided to the participant's parent(s)/LAR(s) to record each study drug intake.

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated by site personnel at visits as indicated in the assessment schedule using the below formula and entered in the eCRF:

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

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

Between visits, compliance is expected to be between 80% and 120%. Compliance values outside of this range will be considered as protocol deviations. The investigator must discuss the non-compliance with the parent(s)/LAR(s) or the participant to clarify the reasons for non-compliance and to take appropriate actions to avoid reoccurrence. This discussion and its outcome must be documented in the source documents. Reasons for non-compliance will also be reported in the eCRF.

5.1.8 Study treatment dose adjustments and interruptions

For participants who are unable to tolerate the protocol-specified dosing scheme, dose adjustments should follow the instructions in the up-titration scheme [Section 5.1.4]. Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruptions of study treatment are described in Section 5.1.10.

If, at any time during the study treatment, the participant experiences an AE (other than criteria B, C, D, or E in Section 5.1.10) in response to which their dose is reduced, re-titration to the iMTD may be resumed, per the investigator's medical judgment. See Section 5.1.4 for up-titration or down-titration.

If study treatment is interrupted by the participant / participant's parent(s)/LAR(s) for any reason, they must immediately inform the investigator.

If a dose of selexipag is missed, participants should take a dose as soon as possible unless the next dose is within the next 6 h. During the up-titration period, the investigator / site staff must ensure that PK samples are collected after 3 days of the same dose and using the same mode of administration.

From Day 1 to Week 16, any dose interruptions (morning and/or evening) must be recorded in the study drug log in the source documents and the eCRF.

After Week 16, interruptions of 1 day or more must be recorded on the study drug log in the source documents and in the eCRF.

In case of permanent discontinuation from study treatment, the EOT visit must occur within 7 days of the discontinuation criterion being met.

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

5.1.9 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the participant's parent(s)/LAR(s), the investigator, the participant (who is developmentally capable to assent or who comes of age), or Sponsor personnel. The main reason for discontinuation of study treatment and whether discontinuation is the decision of the participant's parent(s)/LAR(s) (eg, tolerability- or efficacy-related), the investigator (eg, due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy), or the Sponsor (eg, study terminated) must be documented in the eCRF.

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

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

Study-specific criteria requiring discontinuation of study treatment are described in Section 5.1.10.

A participant who prematurely discontinues study treatment is NOT considered to be withdrawn from the study and will be followed up for safety purposes until 30 days after the last dose of study treatment.

A participant who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered to be withdrawn from the study.

Participants who die or are lost to follow-up are also considered to be withdrawn from the study.

Withdrawal from the study and follow-up medical care of participants withdrawn from the study are described in Sections 8.2 and 8.4, respectively.

5.1.10 Study-specific criteria for pause in up-titration / interruption / premature discontinuation of study treatment

A) Tolerability issues / AEs

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

However, if a participant reaches a dose that cannot be tolerated, the investigator should follow the instructions given in Section 5.1.4.

B) Gastrointestinal ileus or obstruction

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

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

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

C) Hyperthyroidism

Hyperthyroidism has been observed in 1% of the participants treated with selexipag in the GRIPHON study [Uptravi® USPI, Uptravi® SmPC].

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

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

D) Hepatic impairment

If the investigator becomes aware that a participant has developed moderate or severe hepatic impairment (Child-Pugh B or C) at any time during the study, study drug must be permanently discontinued. For participants who develop hepatic impairment at any time during the study, the assessment for hepatic impairment (Child Pugh score, see Section 14.4 Appendix 4) must be done and fully documented.

E) Pulmonary edema due to PVOD

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

F) Treatment with prostacyclin / prostacyclin analogs

If treatment with prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) is initiated at any time during the study (except for acute vasodilator testing during RHC procedure, see also Section 5.2.3), the study drug must be permanently discontinued.

5.2 Previous and concomitant therapy

The use of all study-concomitant therapy (including contraceptives and traditional and alternative medicines, eg, plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous therapy must be recorded in the eCRF if discontinued less than 42 days prior to the signing of the ICF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, and indication will be recorded in the eCRF.

5.2.1 Mandatory treatment

The use of contraceptives is mandated in female subjects of childbearing potential who are heterosexually active because pregnancy increases the risk of disease progression [Bédard 2009] and because there are limited data on the use of selexipag in pregnant women. Although animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, pregnant women were excluded from clinical trials with selexipag.

If hormonal contraceptives are used, they must be initiated at least 30 days before enrollment.

For female subjects who become heterosexually active any time after enrollment and who are of childbearing potential, contraceptives that are immediately effective must be applied as specified in Section 4.5.2.

Contraceptives must be reported in the eCRF.

5.2.2 Allowed concomitant therapy

The PAH-specific therapies allowed as background therapies are ERAs and PDE-5 inhibitors. The dose must have been stable for at least 3 months prior to the first dose of study treatment. For diuretic therapy, the dose must have been stable for at least 1 month prior to the first dose of study treatment.

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

Any change in concomitant therapy or its dose must be recorded in the eCRF.

5.2.3 Forbidden concomitant therapy

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

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

5.3 Treatment of Overdose

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

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

Isolated cases of overdose up to 3,200 µg were reported in adults. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein bound.

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

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until selexipag can no longer be detected systemically (at least 3 days).
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the sponsor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6 STUDY ENDPOINTS

6.1 Pharmacokinetic endpoints

6.1.1 Primary pharmacokinetic endpoint(s)

The primary endpoint is model-based exposure ($AUC_{\tau,ss,combined}$) of selexipag and ACT-333679 corrected for their potency, determined during the 12-week up-titration period. It is compared to the model-based exposure for participants with PAH in GRIPHON. The GRIPHON population PK model will be used and updated based on the acquired pediatric PK data. The model will describe the body weight dependence of the dose-exposure relationship for pediatric participants with PAH [Modeling and Simulation Report, Pediatric dose selection 2016].

6.1.2 Secondary pharmacokinetic endpoints:

- Area under the plasma concentration-time curve over one dosing interval at steady state ($AUC_{\tau,ss}$), maximum plasma concentration at steady state ($C_{max,ss}$), and the time at which $C_{max,ss}$ is observed ($t_{max,ss}$) for selexipag and ACT-333679 based on non-compartmental analysis (NCA).
- Trough concentration at steady state ($C_{trough,ss}$) on Day 15 / Visit 4, and at Week 4 / Visit 5 and Week 6 / Visit 6 for selexipag and ACT-333679.

6.2 Safety endpoints

- Treatment-emergent AEs (TEAEs) occurring up to EOT + 3 days.
- Treatment-emergent SAEs (TESAEs) occurring up to EOT + 3 days.
- AEs leading to permanent discontinuation of study drug.
- Treatment-emergent deaths (all causes) occurring up to EOT + 3 days.
- Treatment-emergent marked laboratory abnormalities (hematology and blood chemistry tests) over time occurring up to EOT + 3 days.
- Change from baseline in selected hematology and blood chemistry laboratory variables over time up to EOT + 3 days.
- Treatment-emergent ECG abnormalities over time occurring up to EOT + 3 days.
- Change from baseline in TSH over time up to EOT + 3 days.
- Change from baseline in vital signs (blood pressure, heart rate) over time up to EOT + 3 days.
- Change from baseline in height and body mass index over time up to EOT + 3 days.
- Change from baseline in sexual maturation (Tanner stage) over time up to EOT + 3 days.

6.3 Exploratory endpoints

- Change from Baseline/Enrollment up to each time point of assessment in modified New York Heart Association (NYHA) / WHO FC.
- Change from baseline up to each time point of assessment in exercise capacity as measured by 6MWD.
- Change from baseline in Panama FC up to each time point of assessment.
- Percent of baseline in plasma NT pro-BNP at each time point of assessment.

- Change from baseline to each time point assessment in Echo variables (imaging and Doppler evaluation):

  Right ventricular systolic pressure.

  Tricuspid annular plane systolic excursion.

  Pulmonary artery acceleration time.

  Left ventricular eccentricity index.

  Right atrial area index (from apical 4 chamber view).

  Tricuspid annular diameter (from apical 4 chamber view).

- Time to the first of the following disease progression events occurring between first study drug dose and EOT + 7 days:

  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 (i.e., shortness of breath/dyspnea, chest pain, cyanosis, dizziness/ near syncope, or fatigue), or
  - New occurrence or worsening of signs of right heart failure not responding to oral diuretics

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

*worsening from baseline.

[#]eg, ERA, PDE-5 inhibitor, prostanoids, prostacyclin receptor (IP receptor) agonist, soluble guanylate cyclase stimulator.

6.4 Other endpoints

- Palatability of selexipag formulation at Day 1, Week 12, and EOT, assessed using a 5-point facial hedonic scale.

- Acceptability of selexipag formulation at Day 1, Week 12, and EOT, as assessed through a 3-point categorical scale as to whether the child swallowed the medication.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 4 and Table 5. For all visits, the participants must be seen on the designated day with an allowed visit window indicated in the tables. An EOT visit must be performed within 7 days of intake of the last dose of study treatment. A safety follow-up call should follow 30 days after this visit, and will be considered the EOS for an individual participant.

All assessments pertaining to a visit should be performed on the same day. If this is not possible, the visit may extend over more than 1 day within the allowed time window.

If study treatment is prematurely discontinued, the EOT visit must take place as soon as possible and no later than 7 days after the last dose of study treatment. A safety follow-up call should follow 30 days after this visit.

Participants who prematurely discontinue study treatment / study participation for any reason before contributing to PK sampling, or for whom PK samples are missing / have been mishandled, may be replaced.

7.1.1 Screening/re-screening

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

It is the responsibility of the investigator/delegate to obtain written informed consent from the parent(s)/LAR(s) of each participant participating in this study after adequate face-to-face explanation of the objectives, methods, and potential hazards of the study. The participant's parent(s)/LAR(s) who agree that their child will participate in the study and the investigator/delegate must sign the ICF (and, if applicable, the participant's assent form) prior to any study-related assessment or procedure.

Participants whose parent(s)/LAR(s) have already signed the ICF (and, if applicable, the participant's assent form) when the enrollment target has been met may still be enrolled.

It is permitted to re-screen participants once, if the reason for non-eligibility was transient (eg, abnormal laboratory test, insufficient wash-out period of a forbidden medication). If a participant is re-screened, only the safety laboratory assessments must be repeated. Re-consent is needed if the initial consent signature is more than 42 days old.

7.1.2 Unscheduled visits

Unscheduled visits can be performed for any reason including (but not limited to) safety issues, PAH worsening, and study drug dispensation. Depending on the reason for the unscheduled visit (eg, AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the eCRF.

If the reason for an unscheduled visit is suspected PAH worsening / PAH disease progression (eg, signs/symptoms denoting PAH worsening or deterioration of WHO FC [refer to Sections 7.2.2.1 and 7.2.2.2]), the investigator determines the main and contributing causes for worsening as per local practice, preferably including the following assessments (these are also recommended even if PAH progression is assessed at a scheduled visit and in case these assessments are not planned for that particular visit):

- Vital signs
- Concomitant medications (including contraceptives)
- PAH-related non-pharmacological intervention
- Signs/symptoms of PAH
- WHO FC and Panama FC
- Main and contributing cause(s) of worsening
- Central laboratory tests including plasma NT-proBNP
- Physical examination
- Echocardiography (central)

The onset date of worsening, the main and contributing cause(s) for worsening are recorded in the eCRF.

The event itself as well as contributing causes unrelated to PAH are reported as AE/SAE.

If RHCs are performed during the study for any medical reason, as judged by the investigator, these results should be recorded in the eCRF.

After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule [Table 4, Table 5].

Table 4 Visit and assessment schedule until Week 16

Period	**Screen-ing**	**Base-line/ Enroll-ment**	**Treatment**													
			Up-titration												**Maintenance**	
Name	**Screening visit / Visit 1**	**Visit 2**	**Visit 3[b] or Tel**	**Visit 4**	Tel.[a] W3	**Visit 5**	Tel.[a] W5	**Visit 6**	Tel.[a] W7	Tel.[a] W8	Tel.[a] W9	Tel.[a] W10	Tel.[a] W11	**Visit 7**	Tel.[a] W14	**Visit 8**
Time	≤ 42 days before Day 1	**Day 1**	**Week 1 Day 5** 1 / + 2 d	**Week 2** Day 15 ± 3 d	Week 3 Day 22 ± 3 d	**Week 4** ± 3 d	Week 5 ± 3 d	**Week 6** ± 3 d	Week 7 ± 3 d	Week 8 ± 3 d	Week 9 ± 3 d	Week 10 ± 3 d	Week 11 ± 3 d	**Week 12** ± 3 d	Week 14 ± 3 d	**Week 16 / M4** ± 3 d
Written informed consent	X															
Inclusion/exclusion criteria (incl. hemodynamics)	X															
Med. History incl. PAH diagnosis	X															
Previous/Concomitant medications	X	X				X		X						X		X
Mod. NYHA/WHO FC	X	X														X
Panama FC	X	X														X
PAH signs/symptoms	X	X														X
PAH-related non-pharmacological interventions		If applicable														
Physical examination	X[l]	X[k]				X[k]								X[k]		X[k]
Growth: Weight and height	X[m]	X												X		X[m]
Vital signs (blood pressure, heart rate)	X	X				X								X		X
ECG		X	X[g]			X								X[g]		X
Echo[n]		X														X
6MWD test[h]		X[i]														X

Period	**Screen-ing**	**Base-line/ Enroll-ment**	**Treatment**													
			Up-titration												**Maintenance**	
Name	**Screening visit / Visit 1**	**Visit 2**	**Visit 3[b] or Tel**	**Visit 4**	Tel.[a] W3	**Visit 5**	Tel.[a] W5	**Visit 6**	Tel.[a] W7	Tel.[a] W8	Tel.[a] W9	Tel.[a] W10	Tel.[a] W11	**Visit 7**	Tel.[a] W14	**Visit 8**
Time	≤ 42 days before Day 1	**Day 1**	**Week 1 Day 5** 1 / + 2 d	**Week 2** Day 15 ± 3 d	Week 3 Day 22 ± 3 d	**Week 4** ± 3 d	Week 5 ± 3 d	**Week 6** ± 3 d	Week 7 ± 3 d	Week 8 ± 3 d	Week 9 ± 3 d	Week 10 ± 3 d	Week 11 ± 3 d	**Week 12** ± 3 d	Week 14 ± 3 d	**Week 16 / M4** ± 3 d
Tanner stage	X															X
Childbearing potential	X	X	X	X		X		X			X			X		X
Pregnancy test (if appl.)[e]	X	X				X				X				X		X
Laboratory test, Hematology/Chemistry[f]	X	X				X								X		X
TSH		X				X								X		X
Thyroid antibodies		X	X when medically indicated													
T3 and T4		X when TSH is abnormal or when medically indicated														
Plasma NT pro-BNP		X														X
Palatability and acceptability of selexipag		X												X		
PK sampling			X[b]	X[c]		X[c]		X[c]						X[d]		
Study drug dispensing		X												X		X
First dose of study drug		X (p.m.)														
Dose titration			X	X	X	X	X	X	X	X	X	X	X	X [j]		
Drug accountability								X						X		X
(Serious) adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Tel. Scheduled telephone call.
b. PK samples will be taken at pre dose, 1, 2, 4, 6, 8 h and 12 h post morning dose of selexipag in the first 5 participants of Cohorts 1 3 (participant should have been at least 3 days on the same dose and mode of administration to reach steady state). The PK sample at 12 h post morning dose must be before the evening dose of selexipag. For the rest of the participants, a phone call will be done instead of a visit.
c. Trough morning PK samples to be collected from all participants prior to dose escalation at Visits 4, 5, and 6 (participant should have been on the same dose and mode of administration for at least 3 days to reach steady state).
d. For all participants of each cohort who did not provide the starting dose profiles: PK samples to be collected at pre dose, 1, 2, 4, 6, 8 h and 12 h post morning dose of selexipag at highest tolerated dose at Week 12 (at least 3 days on the same dose level and mode of administration to reach steady state). The PK sample of 12 h must be before the evening dose of selexipag.
e. Serum pregnancy test to be performed at screening and urine pregnancy tests every 4 weeks until 30 days after study drug discontinuation.
f. Laboratory test (hematology and blood chemistry) will be repeated at Baseline/Enrollment to confirm eligibility only if the last test is available > 2 weeks from Baseline/Enrollment.
g. At Week 1 or at Week 12, an ECG will be performed before drug intake, and two additional ECGs will be performed 2 and 4 h (±15 min) after study drug intake. The ECG should be recorded before the corresponding PK sample is collected.
h. 6MWD in participants of ≥ 6 to < 18 years of age able to understand and perform the test correctly.
i. Conducted within 14 days before Day 1 (Visit 2).
j. Confirmation of iMTD.
k. Physical exam only for areas of interest (general appearance, cardiovascular, and respiratory system).
l. Complete examination.
m. Height required at Screening and Week 16 only.
n. Echocardiography should be performed prior to physical exertion (eg, 6MWT).

6MWD 6 minute walk distance; 6MWT 6 minute walk test; d day(s); appl. applicable; ECG electrocardiogram; h hour(s); iMTD individual maximum tolerated dose; M month; Mod. modified; NT pro BNP N terminal pro b type natriuretic peptide; NYHA New York Heart Association; PK pharmacokinetic(s); Tel. telephone call; TSH thyroid stimulating hormone; W week; WHO FC World Health Organization functional class.

Table 5 Visit and assessment schedule after Week 16

Period	**Site visits for participants during the first 12 months following Week 16 (M4)**	**Site visits for participants after 12 months**	**Phone calls for participants after 12 months**	**Unscheduled visit**	**End-of-Treatment**	**Safety follow-up Tel.**
Name	**Visit 9, 10, 11, 12**	**Visit 13, 14, 15 …**	**Tel.**	**Unscheduled visit**	**EOT**	**EOS**
Time[e]	**Site visits every 3 months (M7, M10, M13, M16)** ± 15 days	**Site visits every 6 months (M22, M28, M34…)** ± 15 days	**Phone call: every 6 months (M19, M25, M31, M37…) alternating with visits** ± 15 days	**If medically indicated** or recommended for assessing PAH progression	**Last dose of study drug** + up to 7 days	**Phone call: 30 days after last dose of study drug** + up to 7 days
Previous/Concomitant medications for PAH	X	X		X	X	
Mod. NYHA/WHO FC	X	X		X	X	
Panama FC	X	X		X	X	
PAH signs/symptoms	X	X		X	X	
PAH-related non-pharmacological interventions	If applicable					
Physical examination	X[c]	X[c]		X	X[c]	
Growth: Weight and height	X	X		X	X	
Vital signs (blood pressure, heart rate,)	X	X		X	X	
Echo	X[d]			X	X	
6MWD test	X[b]	X		X	X	
Tanner stage	X	X				
Childbearing potential	X	X	X	X	X	
Pregnancy test (if appl.)	X	X	X[a]	X	X	X
Laboratory test (Hematology/Chemistry)	X	X		X	X	
TSH	X	X		X	X	
Thyroid antibodies	X when medically indicated					
T3 and T4	X when TSH is abnormal or when medically indicated					
Plasma NT pro-BNP	X	X		X	X	
ECG	X	X			X	
Study drug dispensing	X	X		X		
Drug accountability	X	X		X	X	

Period	**Site visits for participants during the first 12 months following Week 16 (M4)**	**Site visits for participants after 12 months**	**Phone calls for participants after 12 months**	**Unscheduled visit**	**End-of-Treatment**	**Safety follow-up Tel.**
Name	**Visit 9, 10, 11, 12**	**Visit 13, 14, 15 …**	**Tel.**	**Unscheduled visit**	**EOT**	**EOS**
Time[e]	**Site visits every 3 months (M7, M10, M13, M16)** ± 15 days	**Site visits every 6 months (M22, M28, M34…)** ± 15 days	**Phone call: every 6 months (M19, M25, M31, M37…) alternating with visits** ± 15 days	**If medically indicated** or recommended for assessing PAH progression	**Last dose of study drug** + up to 7 days	**Phone call: 30 days after last dose of study drug** + up to 7 days
Palatability and acceptability of selexipag					X	
(Serious) adverse events	X	X	X.	X	X	X
Vital status						X

a. Urine pregnancy tests to be performed monthly, and results to be communicated to site staff by telephone.
b. Only at Month 7 / Visit 9.
c. Physical exam only for areas of interest (general appearance, cardiovascular, and respiratory system).
d. Echo to be done at Month 7 only.
e. One month corresponds to 4 weeks/28 days.

6MWD 6 minute walk distance; appl. applicable; ECG electrocardiogram; EOS End of Study; EOT End of Treatment; FC functional class; M month; Mod. modified; NT pro BNP N terminal pro b type natriuretic peptide; NYHA New York Heart Association; PAH pulmonary arterial hypertension; Tel. telephone call; TSH thyroid stimulating hormone; WHO FC World Health Organization functional class.

7.2 Study assessments

The study assessments are listed in Table 4 and Table 5. The assessments to be performed during each visit are marked with an 'X'.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel) and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF. The following order of assessments is recommended: PK samples, safety assessments, efficacy assessments, other assessments (unless otherwise specified in Table 4 and Table 5 and in the assessment descriptions below).

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

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

- Body weight scale
- Temperature measurement devices for study treatment storage area and freezer.

Calibration certificates / evidence of equipment maintenance of other equipment should be available as per local requirements.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all participants include: age, sex, race, and ethnicity. Relevant medical history / current medical conditions (eg, chronic and ongoing acute conditions, serious past conditions) present before signing the ICF will be recorded on the medical history page. Where possible, diagnoses and not symptoms will be recorded. The presence/absence of Down syndrome is recorded for all participants in the eCRF.

Medical history of special interest will be captured on the specific Medical History eCRF page and includes:

- Disease characteristics such as PAH etiology, PAH diagnosis (mPAP, PAWP [or LAP, or LVEDP], PVRi values assessed by RHC, and date of diagnosis), date of first observed / assumed PAH symptoms, and signs and symptoms of PAH.
- Medical history (previous and ongoing clinically significant diseases).

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

- Reason for screening failure.
- Baseline data collected until confirmation of screening failure.
- If baseline data are available from any central laboratory (eg, physical activity) they will be transferred to the clinical database.

7.2.2 Exploratory assessments

7.2.2.1 Monitoring of disease progression – signs and symptoms of PAH

To standardize assessment of disease progression, investigators will verify the presence/absence of predefined signs and symptoms denoting clinical worsening of PAH.

The presence and absence of signs/symptoms as well as date of new onset or worsening is recorded in the eCRF.

If there is syncope or at least 2 new or worsening signs/symptoms the investigator reports disease progression in the eCRF and performs further exams to determine the cause [refer to Section 7.1.2]. In addition, the occurrence of a new or worsening sign/symptom is reported as Adverse Event in the eCRF.

7.2.2.2 WHO functional class

The WHO FC [see Section 14.1 Appendix 1] and the Panama FC [Section 14.2 Appendix 2] are recorded in the eCRF. The Panama FC is tailored for children up to 16 years of age [Lammers 2011] and thus its assessment will discontinue in children > 16 years of age.

7.2.2.3 NT-proBNP

The quantification of NT pro-BNP plasma levels will be performed by the central laboratory [see contact details on page 2]. Central laboratory data will be automatically transferred from the central laboratory database to the clinical database.

The materials required for NT pro-BNP sampling will be provided to the investigational site before the start of the study.

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

The actual date and clock time of withdrawal of each blood sample is to be entered in the eCRF.

NT pro-BNP central laboratory reports will be sent to the investigator.

7.2.2.4 6-minute walk distance test

The 6MWD test will be performed in children from ≥ 6 to < 18 years able to understand and perform the test correctly [Takatsuki 2013, Douwes 2015].

The 6MWD test is performed and recorded in the eCRF, as indicated in the assessment schedule. The time of the assessment will be recorded in the eCRF.

The 6MWD is a non-encouraged test that measures the distance covered by the participant during a 6-minute walk.

7.2.2.5 Echo/Doppler

Echo/Doppler will be performed at the visits indicated in the assessment schedule and as described in the guidelines and the central reader manual provided separately from this protocol.

The following Echo/Doppler parameters will be measured:

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

Echo/Doppler data are analyzed centrally and will not be recorded in the eCRF.

7.2.2.6 Palatability and acceptability

The palatability of the selexipag formulation will be assessed at the visits indicated in the assessment schedule using a 5-point facial hedonic scale.

For children not able to comply with the instructions of the test, palatability will be indirectly assessed by the participant's parent(s) or LAR(s) or study site personnel [see Section 14.3 Appendix 3].

The site study personnel will record the palatability score corresponding to the smiley face pointed to by the participant or the response provided by participant's parent(s) or LAR(s) or study site personnel in the eCRF.

The acceptability of the selexipag formulation will be assessed through a 3-point categorical scale as to whether the child swallowed the medication at the visits indicated in the assessment schedule.

For all participants, parent(s) or LAR(s) or study site personnel will be asked, following the study drug intake, whether the child swallowed the medication:

a. fully,
b. partially,
c. not at all.

The site study personnel will record the acceptability score corresponding to the response provided by participant's parent(s) or LAR(s) or study site personnel in the eCRF and source documents.

7.2.3 Safety assessments

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

7.2.3.1 Physical examination

Complete physical examination at screening includes the examination of:

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

At subsequent visits, physical examination includes the examination of general appearance and cardiovascular and respiratory systems.

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

Information for all physical examinations must be included in the source documentation at the study site. The observations should be reported according to body system in the eCRF as either normal or abnormal. If an abnormality is found it should be specified on the corresponding eCRF page.

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

Physical examination findings made after the signing of the ICF that meet the definition of an AE [Section 9.1.1] must be recorded on the AE page of the eCRF.

7.2.3.2 Vital signs

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

Systolic and diastolic BP will be measured in a supine or sitting position. It is recommended to allow the participant to rest for at least 5 minutes, and to use the same position (supine or sitting) throughout the study for an individual participant.

It is recommended that the same type of device is used throughout the study for an individual participant. In addition, blood pressure is measured on the same arm for an individual participant throughout the study.

Vital signs are recorded in the eCRF.

7.2.3.3 ECG

A standard 12-lead ECG is performed at Baseline/Enrollment, Visit 3 (only for participants who have PK sampling), Visit 5, Visit 7 (only for subjects who have PK sampling), Visit 8, Visits 9, 10, 11, 12, 13, 14, 15, etc., and EOT. The participant should rest for at least 5 minutes prior to the recording, and should be in a supine position during the recording. The ECG should be performed before the morning dose of study drug is taken.

At Visit 3 or Visit 7, participants will have two additional ECGs 2 and 4 hours (±15 min) after study drug morning dose intake.

Clinically relevant ECG findings that are present prior to the initiation of study drug must be documented in the Medical History section of the eCRF.

Clinically relevant ECG findings observed after study drug initiation that were not present at Screening or that worsened during the study must be reported as AEs as appropriate [see Section 9.1.1].

A central ECG service [see contact details on page 2] will be used for ECG evaluation. Details about the collection of ECG data and the reporting of results and abnormalities can be found in the ECG manual provided to the investigator.

7.2.3.4 Weight and height

Height will be measured using a stadiometer at Screening and at Week 16, every 3 months for 1 year following Week 16, then every 6 months. Body weight will be measured in indoor clothing but without shoes.

Body weight and height are measured and recorded in the eCRF.

7.2.3.5 Tanner stage

Per CHMP Paediatric addendum to the PAH guidelines [EMA/CHMP/213972/2010], the sexual maturation of pediatric participants in long-term studies is of particular importance. Therefore, the Tanner stage [refer to Section 14.5 Appendix 5] is assessed at regular time points during the study.

Tanner stage is assessed in female participants ≥ 8 years of age and in male participants ≥ 9 years of age (i.e., examination is started once they are 8 and 9 years old, respectively). For participants who enter the study below these ages, sexual maturity assessments will start once they reach the ages of 8 or 9 years (for girls and boys, respectively). Tanner stage assessment is stopped once full sexual maturation is reached (if applicable before EOT). (Self-)Assessment of pubertal Tanner stage by parents or participants may be allowed by the study investigator. In this case, the investigator instructs and assists parents / participants on how this should be assessed at each time of the scheduled assessment.

The Tanner stages of puberty in girls are based on breast size and shape and pubic hair distribution. The Tanner stages of puberty in boys are based on the development of the genitalia and pubic hair distribution [Blondell 1999, Marshall 1969, Marshall 1970]. Actual age at milestone attainment may vary among individuals and among different study populations.

The site study personnel will record the Tanner stage in the eCRF.

For frequency of Tanner stage assessments, see schedule of assessments in Table 4 and Table 5.

7.2.3.6 Childbearing potential

Childbearing potential will be assessed at each visit and recorded in the eCRF.

For female participants of childbearing potential, the study personnel will verify at each visit whether the participant has or plans to become heterosexually active. If confirmed, the study personnel will counsel the participant on the appropriate methods of contraception [refer to Section 4.5.2].

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

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

A central laboratory [see central laboratory manual for contact details, page 2] will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

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

Other exceptional circumstances that require the recording of local laboratory results of the parameters are described in Section 7.2.4.2 (with corresponding normal ranges), including hospitalization of the participant due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

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

After Week 16, under specific circumstances (eg, if the participant lives far from the site and cannot return to the site), laboratory samples may be collected at a laboratory close to where the participant lives (satellite laboratory) and sent to the central laboratory for analysis. In such cases, the satellite laboratory must be provided with the central laboratory sampling kits. Shipment of the samples will be organized by the satellite laboratory. If this process is implemented, the satellite laboratory must be identified prior to enrollment of the participant in the study. The supervision of the satellite laboratory remains the responsibility of the PI.

Central laboratory reports will be sent to the investigator. In the case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the Sponsor personnel and the concerned site personnel. Alert flags that will trigger such notifications are displayed in the central laboratory manual, provided separately.

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

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

7.2.4.2 Laboratory tests

Hematology

- Hemoglobin (g/L)
- Hematocrit (L/L)
- Erythrocyte count (10^9/L)
- Leukocyte count with differential counts (10^9/L)
- Platelet count (10^9/L)

Clinical chemistry

- Alanine aminotransferase (U/L)
- Aspartate aminotransferase (U/L)
- Alkaline phosphatase (U/L)
- Total and direct bilirubin (µmol/L)
- Creatinine (µmol/L)
- Creatinine clearance (mL/min)
- Blood urea nitrogen (mmol/L)
- Uric acid (µmol/L)
- Glucose (mmol/L)
- Cholesterol, triglycerides (mmol/L)
- Sodium, potassium, chloride, calcium (mmol/L)
- Albumin (g/L)
- NT-pro BNP (pmol/L)
- TSH (mU/L)
- Thyroid antibodies (U/mL): Measured at Baseline/Enrollment and at subsequent visits only if TSH is abnormal or when medically indicated
- Free T3 and free T4: Measured only if TSH is abnormal or when medically indicated

Up to Week 16, a total of approximately 24 mL of blood are required for hematology and clinical chemistry testing. After Week 16, approximately 4.8 mL of blood are required per visit.

Pregnancy test

A serum pregnancy test for females of childbearing potential will be performed at Screening and a urine test will be performed on Day 1 (Baseline/Enrollment) before dosing and monthly thereafter. If pregnancy is suspected during the study, a serum pregnancy test

must be performed immediately. Results of the urine pregnancy tests performed after Day 1 are not collected in the eCRF.

7.2.5 Pharmacokinetic assessments

7.2.5.1 Pharmacokinetic assessments

PK blood sampling will be done:

- During the first week of study treatment (PK samples will be collected in the first 5 participants treated in Cohorts 1 to 3 at the following time points: pre-dose, 1, 2, 4, 6, 8, and 12 hours post-morning dose of selexipag (participants should have been on the same dose and mode of administration for at least 3 days in order to reach steady state).
- During the up-titration period, $C_{trough,ss}$ PK samples will be collected in all participants prior to dose escalation at Day 15, and Weeks 4 and 6 (participants should have been on the same dose and mode of administration for at least 3 days in order to reach steady state).
- In each cohort, for participants who did not provide samples during the first week of study treatment, PK samples will be collected at Week 12 at steady state at the following time points: pre-dose, 1, 2, 4, 6, 8, and 12 hours post-morning dose of selexipag (participants should have been on the same dose and mode of administration for at least 3 days in order to reach steady state).

For the participant's convenience, an overnight stay at the site may be required before and/or after the PK profile sampling visit.

In total, 10 PK samples (1.2 mL blood/sample) will be collected per participant. The total amount of blood collected from each participant will be 12 mL. This is in accordance with general recommendations that the total blood volume collected within 24 hours for the purpose of a trial in children should not be more than 1% 5% of total body blood volume. Children are assumed to have 75 80 mL blood / kg body weight; i.e., a 9 kg infant is considered to have approximately 720 mL of total blood volume.

Blood sampling will take approximately 1 minute. Table 4 displays the time points at which the PK samples will be taken.

7.2.5.2 Instructions regarding meals

On the day of the PK samples collection (at Visit 3 or Visit 7 and at Visits 4, 5, and 6), the participant's parent(s)/LAR(s) will be instructed that the meal preceding the morning and evening dose should be light.

Dates and time of meals preceding PK samples will be recorded in the eCRF.

7.2.5.3 Procedure for sampling

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

Blood samples of 1.2 mL will be collected by direct venipuncture or via an i.v. catheter in spray-dried lithium heparin-containing Greiner Vacuettes®. Immediately following collection, the tube will be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution and immediately cooled on ice. Within 30 minutes of collection, the blood samples will be centrifuged at approximately 1500 × g / 3000 revolutions per min for 10 minutes, preferably at 4 °C (39.2 °F).

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

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

The date and exact actual clock time of collection of each blood sample will be entered in the eCRF.

For additional details, refer to the laboratory manual.

7.2.5.4 Labeling

The tubes and labels will be provided by the central laboratory. The tubes for PK assessments will be pre-labeled and will carry the following information:

- Actelion Pharmaceuticals Ltd
- Study number: AC-065A203
- Selexipag and ACT-333679
- Type of sample: plasma
- Visit number (eg, Visit 3, Visit 7)
- Scheduled time point (eg, pre-dose, 1 hour post-dose)
- Participant number (eg, 2001 001)

7.2.5.5 Bioanalysis

The concentrations of selexipag (ACT-293987) and ACT-333679 will be determined using a validated liquid chromatography-tandem mass spectrometry assay. The foreseen limit of quantification for both analytes is 0.01 ng/mL. Concentrations will be calculated by interpolation from a calibration curve.

Quality control samples will be used to determine between-run and overall precision and accuracy of the analysis.

7.2.5.6 Shipping procedures

The site staff will be responsible for the shipment of the samples. Samples must be sent to the central laboratory [see contact details on page 2] at time intervals defined in the laboratory manual. The samples, together with the completed shipment forms, must be packed securely in polystyrene insulated shipping containers containing enough dry ice to last for 48 hours.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

For an individual participant, study completion is reached when the EOS follow-up telephone call is completed.

8.2 Premature withdrawal from study

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

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

home), respecting the participant's right to privacy. If the participant is still unreachable after all contact attempts listed above, they will be considered to be lost to follow-up.

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

If, for whatever reason (except death or loss-to-follow-up), a participant is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the participant, collect unused study treatment, and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the participant's medical records but will not be collected in the eCRF. The investigator must provide follow-up medical care for all participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

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

If the study is prematurely suspended or terminated, the Sponsor will promptly inform the investigators, the Independent Ethics Committee / Institutional Review Board (IEC/IRB), and health authorities, as appropriate, and provide the reasons for the suspension or termination.

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

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

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

Any suspension or premature termination of the study must be communicated to the IDMC.

8.4 Medical care of subjects after study completion / withdrawal from study

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

Such care may include:

- Switching to selexipag (Uptravi) if commercially available.
- Recommendation to initiate any PAH-specific treatment, as per investigator's judgment.

Female participants of childbearing potential must use reliable contraceptive methods until 30 days after last intake of selexipag, if heterosexually active. Appropriate counseling regarding the risks of pregnancy and reliable methods of contraception must be ensured.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaint (PQC), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible.

9.1 Adverse events

9.1.1 Definition of adverse events

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

A TEAE is any AE temporally associated with the use of study treatment (from study treatment initiation until 3 days after study treatment discontinuation) whether or not considered by the investigator to be related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.

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

Overdose, misuse, and/or abuse of selexipag and study treatment errors will be reported as an AE.

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

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

9.1.2 Intensity of adverse events

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

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required to be reported.

For AEs ongoing at the start of study treatment, if the intensity worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

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

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

9.1.3 Relationship to study treatment

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

9.1.4 Reporting of adverse events

All AEs with an onset date after the signing of the ICF and up to EOS must be recorded on specific AE pages of the eCRF.

9.1.5 Follow-up of adverse events

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

AEs still ongoing after EOS must be followed up until they are no longer considered clinically relevant (eg, until symptom resolution) or until stabilization. The follow-up information obtained after a participant's EOS is recorded in the participant's medical chart (source data), but is not recorded in the eCRF.

9.2 Serious adverse events

9.2.1 Definitions of serious adverse events

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

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

The following reasons for hospitalization are not considered SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, eg, hospitalization for coronary angiography in a participant with stable angina pectoris.

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

9.2.2 Reporting of serious adverse events

All SAEs occurring after the signing of the ICF up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE notification

form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

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

9.2.3 Follow-up of serious adverse events

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

9.2.4 After the 30-day follow-up period

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

9.2.5 Reporting procedures

All SAEs, including PQC, must be reported by the investigator to the Sponsor within 24 hours of the investigator's first knowledge of the event.

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

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

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

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

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

The expectedness of an adverse reaction is determined by the Sponsor in the reference safety information (RSI) section provided in the most recent version of the selexipag IB.

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

9.3 Pregnancy

If a female participant becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. This counseling comprises all medications administered at that time and follows the instructions of the respective approved drug labels.

9.3.1 Reporting of pregnancy

Any pregnancy occurring after study start (i.e., signing of the ICF) in female participants or partners of male participants up to 30 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies of female participants and partners of male participants must be reported on the Pregnancy notification and follow-up forms, which are sent to the Sponsor, and on an AE page in the eCRF.

9.3.2 Follow-up of pregnancy

Any pregnancies must be followed-up to their conclusion and the outcome must be reported to the Sponsor.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE notification form as described in Section 9.3.1.

9.4 Special Reporting Situations

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

- Overdose of a sponsor study treatment (see Section 5.3)
- Suspected abuse/misuse of a sponsor study treatment

- Accidental or occupational exposure to a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without participant exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

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

9.5 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, Tanner stage, growth, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the responsible Sponsor Clinical Team (in charge of ensuring participants' safety as well as data quality). In addition, an IDMC monitors safety data [see Section 3.3]. The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (eg, medical imaging, local laboratory values) for the purpose of safety monitoring. Such additional data may be shared with external experts appointed by the Sponsor of this study.

9.6 Product quality complaint handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

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

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

Contacting Sponsor Regarding Product Quality

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

10 STATISTICAL METHODS

All statistical analyses will be conducted by the Sponsor or by designated contract research organizations (CROs) supervised by the Sponsor.

A Statistical Analysis Plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations. All statistical analyses will be performed by age cohort and overall.

10.1 Analysis Sets

10.1.1 Screened Analysis Set

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

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled participants who were eligible to receive the study drug.

10.1.3 Pharmacokinetic Analysis Set

The PK Analysis Set (PKS) comprises all participants included in the Safety Set who complied with the protocol sufficiently and did not deviate from the protocol in a way that might affect the PK outcome of the study. The criteria for sufficient compliance include exposure to treatment, availability of PK measurements, and absence of major protocol deviations that have an impact on the PK. The full list of criteria will be detailed in the modeling data analysis plan and the SAP.

10.1.4 Safety Analysis Set

The Safety Analysis Set includes all participants who received at least one dose of study treatment.

10.1.5 Usage of the analysis sets

The FAS is used for the analyses of exploratory efficacy variables as well as for the description of the study population at baseline. Unless otherwise specified, individual listings are prepared on the FAS.

The PKS is used for the analysis of the primary and secondary PK variables.

The Safety Analysis Set is used for the analysis of the safety variables and other variables.

The Screened Analysis Set is used for the description of participant disposition.

10.2 Variables

10.2.1 Primary pharmacokinetic variable(s)

10.2.1.1 PK analysis and modeling

The primary endpoint is model-based exposure ($AUC_{\tau,ss,combined}$) of selexipag and ACT-333679 weighted by their potency determined during the 12-week up-titration period [Modeling and Simulation Report, Pediatric dose selection 2016]. The population PK model in the GRIPHON study will be updated with observed data in this study during interim and final PK analyses in order to determine the model-based exposure ($AUC_{\tau,ss,combined}$) [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014].

For each interim analysis and the final analysis, the available pediatric data will be pooled and the population PK model re-estimated to properly describe the dose-exposure relationship in dependence with body weight. PK information from the adult population will be incorporated by pooling the data or using current parameter estimates as priors when updating the model.

More detail will be described in the modeling data analysis plan, which will be finalized before the PK interim analysis 1 and any update thereof.

10.2.2 Secondary pharmacokinetic variables

- Plasma concentrations at trough at Visits 4, 5, and 6.
- $AUC_{\tau,ss}$, $C_{max,ss}$, and $t_{max,ss}$ for selexipag and ACT-333679 based on NCA.

10.2.3 Exploratory pharmacokinetic / pharmacodynamic analysis

The PK/pharmacodynamic (PD) relationships will be investigated by population PK/PD modeling. Details will be in the modeling data analysis plan.

10.2.4 Safety variables

The safety variables described below are related to the safety endpoints described in Section 6.2. Baseline is defined as the last non-missing value observed before or on the day of the first study drug intake.

The safety variables are the following:

- TEAEs occurring up to EOT + 3 days.
- TESAEs occurring up to EOT + 3 days.

- AEs leading to permanent discontinuation of study drug.
- Treatment-emergent deaths (all causes) occurring up to EOT + 3 days.
- Treatment-emergent marked laboratory abnormalities (hematology and blood chemistry tests) over time occurring up to EOT + 3 days.
- Change from baseline in selected hematology and blood chemistry laboratory variables over time up to EOT + 3 days.
- Treatment-emergent ECG abnormalities over time occurring up to EOT + 3 days.
- Change from baseline in TSH over time up to EOT + 3 days.
- Change from baseline in vital signs (blood pressure, heart rate) over time up to EOT + 3 days.
- Change from baseline in height and body mass index over time up to EOT + 3 days
- Change from baseline in sexual maturation (Tanner stage) over time up to EOT + 3 days.

10.2.5 Exploratory efficacy variables

Exploratory variables described below are related to the exploratory endpoints described in Section 6.3.

The exploratory variables are the following:

- Time to disease progression / clinical worsening from first study drug dose up to EOT + 7 days.
- Change from Baseline/Enrollment up to each time point of assessment in modified NYHA/WHO FC, classified as worsened (> baseline value), unchanged (baseline value), or improved (< baseline value).
- Change from baseline over time up to each time point of assessment in exercise capacity as measured by 6MWD.
- Change from baseline in Panama FC up to each time point of assessment, classified as worsened (> baseline value), unchanged (baseline value), or improved (< baseline value).
- Percent of baseline in plasma NT pro-BNP at each time point of assessment.
- Change from baseline up to each time point of assessment in Echo variables (imaging and Doppler evaluation):

  Right ventricular systolic pressure.

Tricuspid annular plane systolic excursion.

Pulmonary artery acceleration time.

Left ventricular eccentricity index.

Right atrial area index (from apical 4 chamber view).

Tricuspid annular diameter (from apical 4 chamber view).

10.2.6 Other variables

Other variables are related to the other endpoints described in Section 6.4.

The other variables are:

- Palatability of selexipag formulation at Day 1, Week 12, and EOT, assessed using a 5-point facial hedonic scale.
- Acceptability on selexipag formulation at Day 1, Week 12, and EOT, as assessed through a 3-point categorical scale as to whether the child swallowed the medication.

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

Not applicable.

10.3.2 Analysis of the primary pharmacokinetic variable(s)

10.3.2.1 Hypotheses and statistical model

Not applicable.

10.3.2.2 Handling of missing data

Not applicable.

10.3.2.3 Main analysis

The observed PK data will be described by a population PK model using the same model structure as for the adult participants with PAH in the GRIPHON study [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014, Modeling and Simulation Report, Pediatric dose selection 2016]. This population PK model describes the PK of selexipag and ACT-333679 by 2-compartmental distribution models with linear elimination. Selexipag is absorbed by a first order process and part of the elimination from the central compartment is a metabolic transformation to form ACT-333679 [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014].

The analyses will be performed to confirm or potentially revise the starting doses and up-titration increments for the next age cohort and the starting dose of the Phase 3 study.

10.3.2.4 Supportive/sensitivity analyses

Not applicable.

10.3.3 Analysis of secondary pharmacokinetic variable(s)

Plasma concentrations will be summarized per time point, by dose and body weight cohort using arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and two-sided 95% CI of the mean.

$AUC_{\tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$, and $t_{max,ss}$[9] for selexipag and ACT-333679 based on NCA for selexipag and ACT-333679 will be listed and summarized by dose and body weight cohort, with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, coefficient of variation in %, and 95% CI of the arithmetic and geometric means.

Dose proportionality for $AUC_{\tau,ss}$ and $C_{max,ss}$ of selexipag and ACT-333679 will be explored by the power model as described by [Gough 1995].

10.3.4 Exploratory pharmacokinetic / pharmacodynamic analysis

The population PK/PD model will be built based on individual predictions of steady-state exposure for iMTD based on the final population PK models for both selexipag and ACT-333679. More details on PK and PD analyses will be in the modeling data analysis plan.

10.3.5 Analysis of the safety variable(s)

All analyses of safety variables will be carried out descriptively using the Safety Analysis Set and will be performed as follows:

- In the overall population.
- By iMTD dose groups.
- By age cohort.

The iMTD is defined as the last dose received before the Week 12 visit (for participants who prematurely discontinued study drug) or the dose received on the day of the Week 12 visit (for participants who completed the 12-week up-titration period).

Safety data will also be explored by age cohort and by iMTD dose groups if a sufficient number of participants allows.

10.3.5.1 Treatment-emergent adverse events

The number and percentage of participants with at least one TEAE / TESAE / AE leading to study treatment discontinuation will be described by system organ class (SOC) and

[9] The geometric mean of t_{max} and its 95% CI will not be calculated.

preferred term (PT) up to EOT + 3 days, and separately for the up-titration period (up to Week 12) and the maintenance phase (> Week 12 up to EOT + 3 days).

The same analysis will be performed according to the maximum intensity of reported AEs and according to the relationship to the study drug.

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

10.3.5.2 Treatment-emergent death

The number and percentage of treatment-emergent deaths will be described by SOC and PT up to EOT + 3 days.

In addition, all deaths reported during the study will be listed.

10.3.5.3 Laboratory variables

All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments. All recorded assessments will be assigned to the most appropriate visit time points according to the best fitting time-window for that assessment using the usual location and scale summary statistics.

For each laboratory variable, the number and percentage of participants with at least one treatment-emergent marked abnormality will be summarized up to EOT + 3 days.

The change in selected laboratory values and the change in TSH will also be summarized over time up to EOT + 3 days, using the same descriptive statistics for continuous variables.

10.3.5.4 ECG

For each ECG variable, the number and percentage of participants with at least one treatment-emergent marked abnormality will be summarized up to EOT + 3 days.

10.3.5.5 Vital signs

Absolute values and changes from baseline will be summarized over time up to EOT + 3 days, using descriptive statistics for continuous variables.

10.3.5.6 Height and Weight

Absolute values and changes from baseline will be summarized over time up to EOT + 3 days, using descriptive statistics for continuous variables.

10.3.5.7 Sexual maturation

Absolute values and changes from baseline will be summarized over time up to EOT + 3 days, using descriptive statistics for continuous variables.

10.3.6 Analysis of the exploratory efficacy variables

All analyses of exploratory variables will be carried out descriptively using the FAS and will be performed as follows:

- In the overall population.
- By iMTD dose groups.
- By age cohort.

The main exploratory analysis will be based on observed data, with no imputation rules. Sensitivity analyses will be performed by imputing missing values as appropriate and will be described in the SAP.

10.3.6.1 Time to disease progression / clinical worsening

Event time is defined as the time elapsed from the first study drug administration to the day of the occurrence of the event. Time to event endpoints will be presented as Kaplan Meier estimates with two-sided 95% CLs at relevant time points 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 Sets) and a tabular form. Participants who did not experience an event will have their event time censored at EOT + 7 days. The number of participants at risk, the number of participants censored and the number of participants with event will be displayed.

10.3.6.2 NYHA / WHO FC

The proportion of participants having worsened, remained unchanged, or improved will be calculated at each time point of assessment and up to the timepoint with at least 10 participants in the cohort. Two-sided 95% CIs of the proportions will be presented.

10.3.6.3 6MWD

The change from baseline will be summarized at each time point of assessment up to the timepoint with at least 10 participants in the cohort, using descriptive statistics for continuous variables. Two-sided 95% CIs of the mean and median will also be provided.

10.3.6.4 Panama FC

The proportion of participants having worsened, remained unchanged, or improved will be calculated at each time point of assessment up to the timepoint with at least 10 participants in the cohort. Two-sided 95% CIs of the proportions will be presented.

10.3.6.5 NT-proBNP

The percent of baseline will be summarized at each time point of assessment and up to the timepoint with at least 10 participants in the cohort, using descriptive statistics for continuous variables on the log-transformed data. The resulting mean and two-sided 95%

CIs will be inversely transformed using the exponential function to provide the geometric mean and corresponding two-sided 95% CIs.

10.3.6.6 Echo/Doppler

The change from baseline to each time point of assessment for each Echo/Doppler variable will be summarized at each point of assessment up to the timepoint with at least 10 participants in the cohort, using descriptive statistics for continuous variables. The two-sided 95% CIs of the means will also be provided.

10.3.7 Analysis of the other variables

All analyses of other variables will be carried out descriptively using SAS (Statistical Analysis System) and will be performed as follows:

- In the overall population.
- By iMTD dose groups.
- By age cohort.

The iMTD is defined as the last dose received before the Week 12 visit (for participants who prematurely discontinued study drug) or the dose received the day of the Week 12 visit (for participants who completed the 12-week up-titration period).

10.3.7.1 Palatability and acceptability

The palatability and acceptability of selexipag will be summarized separately with counts and percentages.

10.4 Interim analyses

An IDMC will be involved in the study to periodically review safety data and, if requested, PK data [see Section 3.3].

As described in Section 3.1, two interim PK analyses will be performed. They will be detailed in the modeling data analysis plan.

Additional assessments of PK profiles and interim analyses may be performed, as deemed appropriate by the sponsor.

10.5 Sample size

Based on clinical trial simulations using the population PK model of the GRIPHON study, at least 15 participants between ≥ 12 and < 18 years of age (Cohort 1), at least 15 participants between ≥ 6 and < 12 years of age (Cohort 2), and 10 participants between ≥ 2 and < 6 years of age (Cohort 3) with evaluable PK profiles are necessary to obtain a 90% confidence interval of the $AUC_{\tau,ss,combined}$ within a 1.4-fold range above or below the predicted median [see Section 14.7 Appendix 7].

PK data of pediatric participants with PAH in the planned clinical trial were simulated using the GRIPHON population PK model by appropriate assumptions of body weights. The body weight impact on PK model parameters was used as determined based on adult data. PK parameters were re-estimated 100 times and $AUC_{\tau,ss,combined}$ was simulated 1,000 times, taking the parameter estimation uncertainty into account to determine $AUC_{\tau,ss,combined}$ prediction uncertainty. This assessment of the $AUC_{\tau,ss,combined}$ prediction uncertainty was performed for each planned interim analysis and the final analysis to check that at each stage the $AUC_{\tau,ss,combined}$ for the respective cohort could be determined with sufficient accuracy.

The sample size is determined based on the assumption that the PK characteristics have the same inter-individual variability in pediatric as in adult participants with PAH. Furthermore, it is assumed that pediatric participants with PAH of the same weight as adult participants with PAH have the same PK, as relevant metabolic and elimination pathways are assumed to be mature and thus the PK modeling can partly be built on results from the GRIPHON study. At the interim analyses and the final PK analysis, all available PK data will be used to update the PK model and to confirm or adjust the dose selection. The emerging results will also be used to reconsider the sample size, with the aim of minimizing it. However, if the quality of the data collected does not allow for a sufficiently precise confirmation of body weight-based doses, additional participants may need to be enrolled in the study. More details on interim analyses will be provided in the modeling data analysis plan.

Based on the pediatric PK data available at the second interim analysis, the planned sample size for Cohort 3 (N 10) was assessed using a simulation/estimation approach. Pediatric datasets were simulated with fold-deviations of exposures ($AUC_{\tau,ss,combined}$) of 0.5, 0.7, 1, 1.3, and 1.5-fold compared to the adult reference model [PK Interim Analysis Report-2 AC-065A203 2020]. Based on this analysis, the power of recognizing a pediatric to adult ratio of 0.5, 0.7, 1.3, and 1.5 as significantly different from 1, is predicted to be >99%, 82.8%, 56.4%, and 83.2%, respectively. Type 1 error (i.e., when the AUC ratio is 1) is estimated to be 11.8%. If the sample size of Cohort 3 is increased to 15, the estimated values of the power are predicted to be >99%, 91.6%, 71.2% and 96.2% for the exposure ratios of 0.5, 0.7, 1.3, and 1.5, respectively, and the Type 1 error is estimated to be 11.0% [PK Interim Analysis Report-2 AC-065A203 2020]. Based on this assessment, the planned sample size for Cohort 3 has been increased to at least 15 PK evaluable participants in order to ensure a power of at least 70% for all potential outcomes.

11 DATA HANDLING

11.1 Data collection

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

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

Entries recorded by the participant or by the participant's parent(s)/LAR(s) in the Study Drug Diary are considered source data. Site personnel will review and ensure completeness and readability of the participants' entries.

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

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

11.2 Maintenance of data confidentiality

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

11.3 Database management and quality control

eCRFs will be used for all participants. The investigators will have access to the site eCRF data until the database is closed. Thereafter, they will have read-only access. The eCRF

must be kept current to reflect participant status at any time point during the course of the study.

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

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

ECGs and Echos will be read centrally by a central reader and the results will be sent electronically to the Sponsor.

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

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the Sponsor's appropriate Quality System documents. After database closure, the investigator will receive the eCRFs of the participants of their site (including all data changes made) on electronic media or as paper copies.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

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

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the parent(s)/LAR(s) and the participant (such as the ICF, the Assent, the scales, the study drug diary) to an IEC/IRB. Approval from the committee/board must be obtained before starting

the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

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

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

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

12.3 Informed consent

Pediatric participants are legally unable to provide informed consent. Therefore, full informed consent must be obtained from parent(s) or an LAR.

It is the responsibility of the investigator/delegate to obtain informed consent from the participant's parent(s)/LAR(s) and the assent by the child according to ICH-GCP and Declaration of Helsinki guidelines and local regulations. The investigator/delegate must explain to the parent(s)/LAR(s) and the child that they are completely free to refuse to enter the study or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific participant populations and of individual participants, as well as to the methods used to give the information. Adequate time shall be given for the participant, the parent(s) and/or LAR(s) to consider their decision to participate in the study and it shall be verified that the participant has understood the information (eg, by asking the participant and/or the parent(s)/LAR(s) to explain what is going to happen).

Assent must be obtained from study participants who are developmentally capable. The criteria for developmental capability to give assent follows local requirements. Distinct assent forms are provided per age category according to local practice. Participants who come of age during their study participation must consent to continuing their participation in the study. The age when participants are considered capable of giving informed consent must follow local regulations.

The ICF will be provided in the country local language(s).

Site personnel (according to local regulation) authorized to participate in the consent process and/or to obtain consent from the participant's parent(s)/LAR(s) and/or participant

will be listed on the Delegation of Authority form supplied by the Sponsor. A study physician must always be involved in the consent process.

The participant's parent(s)/LAR(s) and authorized site personnel listed on the Delegation of Authority form supplied by the Sponsor must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin.

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

12.4 Indemnification, compensation, and refund of expenses to subjects' parent(s)/LAR(s) and investigators

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

The indemnification of the participant's parent(s)/LAR(s) in the event of study-related injuries will comply with applicable regulations.

Participant's parent(s)/LAR(s) will be reimbursed for the study-related expenses (eg, travel costs, meals, hotels) and may be offered financial compensation for their participation in the study only to the extent permitted by applicable local regulations.

12.5 Protocol adherence/compliance

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

If a protocol deviation occurs, the investigator/delegate will inform the Sponsor or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of

ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to the Sponsor's or (overruling) local requirements.

All protocol deviations will be reported by the CRA into the Clinical Trial Management System (CTMS). Major protocol deviations will be reported in the CSR. IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

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

12.7 Essential documents and retention of documents

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

These records are to be classified into two different categories of documents: Investigator Site File (ISF) and participants' source documents.

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

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

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

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

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

12.8 Monitoring

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

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

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

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

The PI must ensure that the eCRF is completed after a participant's visit (site visit or telephone call), and that all requested participant files (eg, ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by

the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the participant is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

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

12.9 Investigator Site File

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

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

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

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

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

12.10 Audit

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

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

12.11 Inspections

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

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

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

12.12 Reporting of study results and publication

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

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

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

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

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

- Substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- Drafting of the publication or critical review for important intellectual content; and
- Providing final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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14 APPENDICES

14.1 Appendix 1 WHO Functional Class

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

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

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

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

14.2 Appendix 2 Panama Functional Class For Pediatrics

For children aged 2 5 years

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

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

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

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

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

For children aged 5 16 years

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

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

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

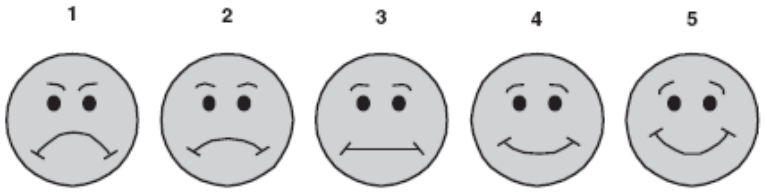
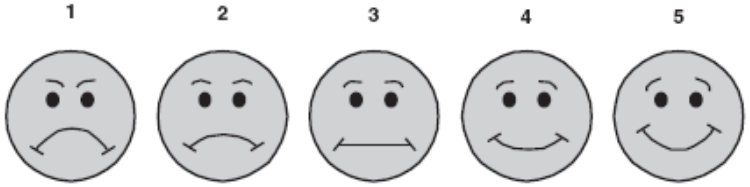
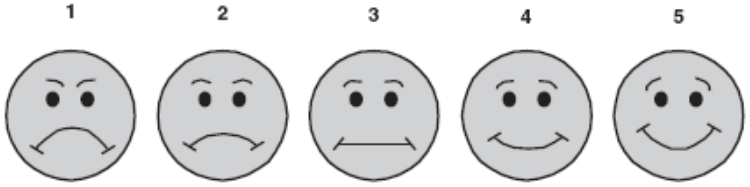
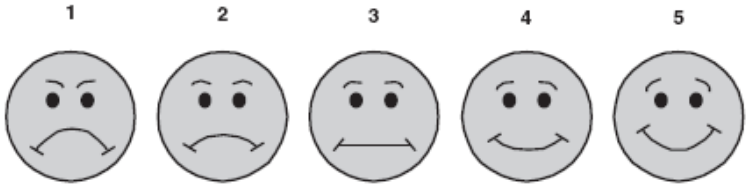
Class IIIb Unable to attend school, but mobile at home and interacting with friends. Wheelchair needed outside the home. Growth compromised. Poor appetite. Supplemental feeding. Less than ordinary activity (eg, dressing) causes undue

dyspnea, fatigue, syncope and/or presyncope, or chest pain. Plus features of Class IIIa.

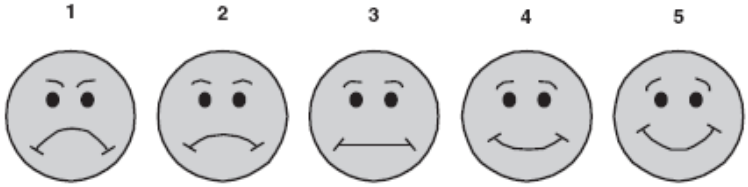
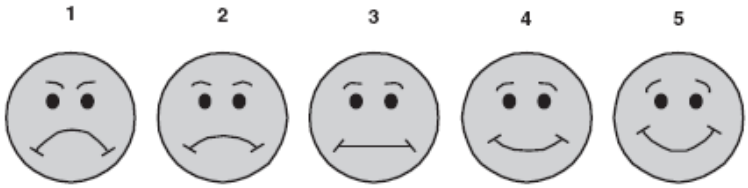
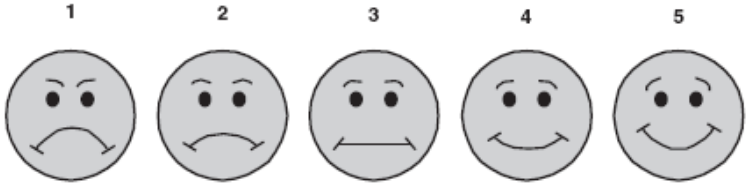
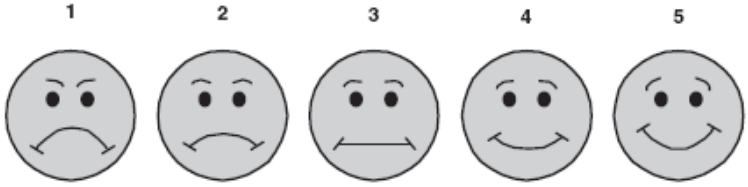
Class IV Unable to carry out any physical activity without undue dyspnea, fatigue, syncope, or chest pain, unable to attend school, wheelchair dependent, not interacting with friends. Syncope and/or right heart failure. Plus features of Class III.

14.3 Appendix 3 Palatability And Acceptability Of Selexipag

PALATABILITY QUESTIONNAIRE FOR SUBJECTS

1.	How much do you like the taste of this medicine?	 Dislike very much / Dislike a little / Not sure / Like a little / Like very much
2.	How easily can you swallow this medicine?	 Very difficult / Difficult / OK / Easy / Very easy
3.	How much do you like that this medicine is taken twice every day?	 Dislike very much / Dislike a little / Not sure / Like a little / Like very much
4.	How easy is it to remove the medicine from the packaging?	 Very difficult / Difficult / OK / Easy / Very easy

PALATABILITY QUESTIONNAIRE FOR CAREGIVERS/SITE PERSONNEL

1.	On the basis of reaction/ facial expression of your child, how much do you believe your child likes the taste of this medicine?	 1 = Dislike very much; 2 = Dislike a little; 3 = Not sure; 4 = Like a little; 5 = Like very much
2.	On the basis of reaction/ facial expression of your child, how easily can your child swallow this medicine?	 1 = Very difficult; 2 = Difficult; 3 = OK; 4 = Easy; 5 = Very easy
3.	How much do you like that this medicine is given twice every day?	 1 = Dislike very much; 2 = Dislike a little; 3 = Not sure; 4 = Like a little; 5 = Like very much
4.	How easy is it to remove the medicine from the packaging?	 1 = Very difficult; 2 = Difficult; 3 = OK; 4 = Easy; 5 = Very easy

14.4 Appendix 4 Child-Pugh Classification

The Child-Pugh classification will be used to assess the severity of the liver disease according to the following table [adapted from FDA 2003 and Vincent 2012]:

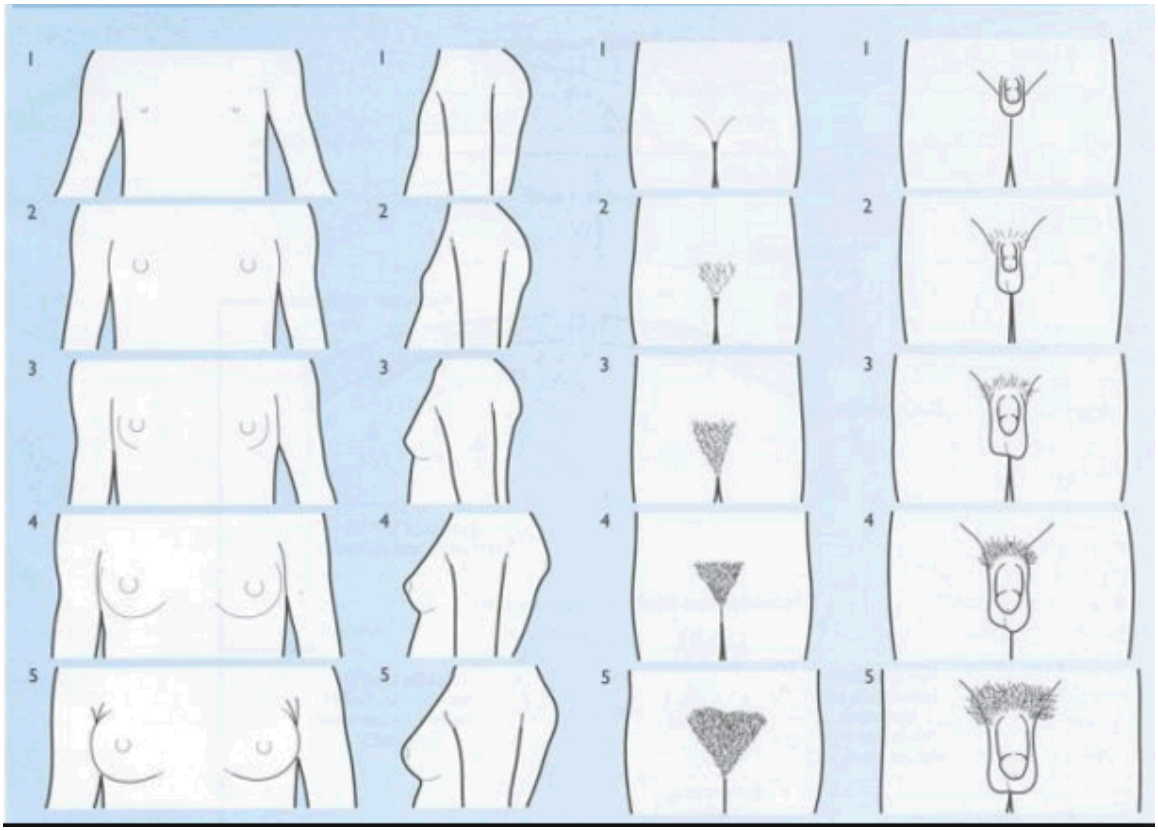
Table 6 Child Pugh Classification

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

*Hepatic encephalopathy scoring will be based on the following criteria:
• Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram
• Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
• Grade 2: lethargic, time disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
• Grade 3: somnolent, stuporous, place disoriented, hyperactive reflexes, rigidity, slower waves
• Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 3 cycles per second delta activity

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

14.5 Appendix 5 Tanner Scale



Illustrated by Michal Komorniczak (Poland)

14.6 Appendix 6 Echo/Doppler

The parameters will be assessed as per Echo image acquisition guidelines.

14.7 Appendix 7 Sample Size Calculation Related To Dosing Scheme Confirmation In Pediatric PK Study

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LIST OF ABBREVIATIONS

$AUC_{\tau,ss}$	Area under the plasma concentration vs time curve over one dosing interval at steady-state
$AUC_{\tau,ss,combined}$	Combined exposure over one dosing interval at steady-state
CL	Clearance (selexipag)
df	Degree of freedom
FIM	Fisher information matrix
GRIPHON	Prostacyclin (PGI_2) Receptor agonist In Pulmonary arterial HypertensiON (study acronym)
IIV	Inter-individual variability
k_{12}	Transfer rate constant central to peripheral volume selexipag
k_{21}	Transfer rate constant peripheral to central volume selexipag
k_{34}	Transfer rate constant central to peripheral volume ACT-333679
k_{43}	Transfer rate constant peripheral to central volume ACT-333679
k_a	Absorption rate constant
k_m	Elimination rate (ACT-333679)
k_{met}	Metabolism rate constant selexipag to ACT-333679
N	Sample size
NCA	Non-compartmental analysis
PAH	Pulmonary arterial hypertension
PK	Pharmacokinetic(s)
RSE	Relative standard error
T_{lag}	Absorption lag time
V_m	Volume of the central compartment for ACT-333679
V_p	Volume of the central compartment for selexipag
α	Significance level

β	Power
Δ	Log-transformed fold-difference
σ	Population standard deviation

14.7.1 INTRODUCTION

In the revised Pediatric Investigation Plan, Actelion proposes to conduct a global Phase 3 pediatric study to demonstrate the safety and effectiveness of selexipag to treat pulmonary arterial hypertension (PAH) in children from 2 years to less than 18 years of age. Dose selection for this future study will be based on data from a pharmacokinetic (PK) study in pediatric PAH patients. The analyses documented here aim to establish the sample size for the PK study to provide sufficient confidence in the selection doses for the future study.

The selection of the starting dose for the first study of selexipag in children is aimed to provide the same overall drug exposure in pediatrics than in adults, with gradual up-titration according to individual tolerability. Starting doses have been calculated based on body weight, using the adult population PK model obtained from the GRIPHON study [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014, Modeling and Simulation Report, Pediatric dose selection 2016], to achieve the same exposure as the starting selexipag dose for adults. Exposure is defined as the combined steady-state exposure to selexipag and its ACT-333679 metabolite over one dosing interval ($AUC_{\tau,ss,combined}$). The $AUC_{\tau,ss,combined}$ is the sum of the selexipag and ACT-333679 exposures weighted by their potency ratio. The data collected in the pediatric study phase 2 will be used to confirm or adjust the selection of the selexipag starting dose for the Phase 3 study.

The participants will be enrolled in the PK study in three age cohorts starting with participants of 6 years and older, i.e., with Cohort 1. After an interim analysis of the data from Cohorts 1 and 2, the children of Cohort 3 ($\geq$ 2 to < 6 years of age) will be included in the study. The model-based interim analysis will confirm or potentially adjust the selection of the starting doses for the last cohort.

For each pediatric participant, a PK profile (pre-dose, 1, 2, 4, 6, 8, and 12 hours after dosing) will be assessed either at the starting dose or at Week 12 at which the individual maximum tolerated dose for each participant must be finally determined. In addition, 3 trough samples will be taken at intermediate doses at steady state.

The sample size per cohort of pediatric participants ($\geq$ 12 to < 18 years, $\geq$ 6 to < 12 years, $\geq$ 2 to < 6 years) is evaluated based on the precision to predict the $AUC_{\tau,ss,combined}$ expressed as -fold over the median. Two approaches of sample size calculations were performed depending on the method used to analyze the PK data obtained. First, the sample size per age cohort was calculated based on a t-distribution of the log-transformed observed $AUC_{\tau,ss,combined}$ values, obtained by the non-compartmental analysis (NCA) method. Second, clinical trial simulations using the GRIPHON population PK model [Modeling and Simulation Report AC-065A302 (GRIPHON) 2014] were performed and the uncertainty to estimate the model parameters and predict the $AUC_{\tau,ss,combined}$ was

determined. These trial simulations were performed for planned interim analyses and the final analysis using the pooled data from all age cohorts.

14.7.2 Analysis

14.7.2.1 Sample size calculations based on observed $AUC_{\tau,ss,combined}$ (NCA analysis)

Based on each patient's profile, the $AUC_{\tau,ss,combined}$ can be derived by NCA and normalized to the dose the patient received when the profile was assessed. The sample size should be large enough to determine the mean exposure of an age cohort with sufficient precision.

Assuming a t-distribution for the log-transformed $AUC_{\tau,ss,combined}$ values, sample sizes can be calculated as the minimal number N for which the following equation holds true:

$$N \geq \frac{\sigma^2 \cdot \left(t_{1-\alpha/2,df} + t_{1-\beta/2,df}\right)^2}{\Delta^2}$$

where t is the quantile of the t-distribution [Bock 1998] with a $df = N - 1$ as the degree of freedom. The significance level α and the power β are set to 5% and 80%, respectively. The population standard deviation σ is assumed to be equal to the standard deviation of the log-transformed $AUC_{\tau,ss,combined}$ for the adult PAH patients in GRIPHON study, i.e., 0.6, and the difference Δ to be detected is the log-transformed fold difference. Table 1 shows the sample sizes for different fold differences. To detect a 1.4 fold-difference as suggested by a draft FDA guideline [FDA 2014], the required sample size of 30 participants is infeasible for a PK study considering the rareness of pediatric PAH. However, a sample size of 10 participants per age group would still be able to detect a 2-fold difference.

Table 1 Sample sizes for each age cohort based on a t-distribution for log-transformed $AUC_{\tau,ss,combined}$

Fold difference	*Sample size based on Bock 1998*
1.4	30
1.75	15
2	10

14.7.2.2 Sample size calculations based on clinical trial simulations (model-based analysis)

A PK study with 15 patients in Cohort 1 and Cohort 2, respectively, and 10 patients in Cohort 3 was evaluated in a model-based approach by clinical trial simulations. According to the analysis based on observed $AUC_{\tau,ss,combined}$ described above, prediction uncertainties would be limited to 1.75- to 2-fold. Considering the rareness of pediatric PAH higher participant numbers do not seem reasonable. Using a model-based approach that pools data from all cohorts and adds PK information from adult PAH participants, the acquired PK data can be utilized better.

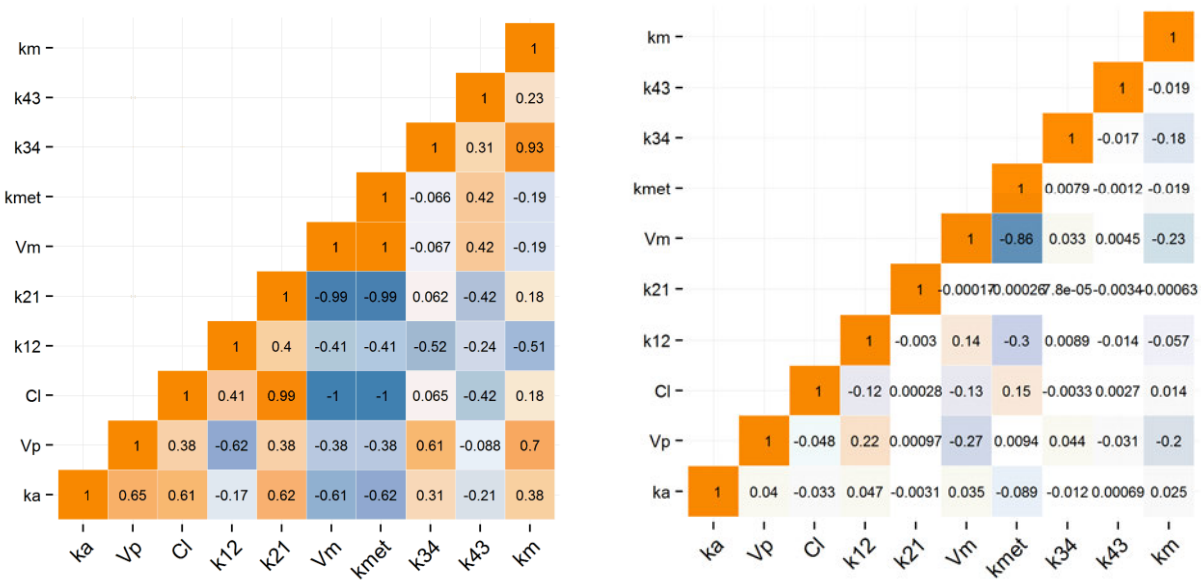
14.7.2.2.1 Preparatory assessments based on the Fisher information matrix

Before performing clinical trial simulations, the identifiability of the model parameters and an estimate on required sample sizes were assessed based on the Fisher information matrix (FIM). The FIM was derived using PFIM, an R-based software to assess the FIM for population PK models [Bazzoli 2010].

Model parameters were set to the estimates obtained in the GRIPHON population PK analysis. The absorption time lag (T_{lag}) was not included in order to simplify the model implementation in PFIM. This has no effect on the results regarding the identifiability of parameters that impact the AUC, since the time lag only constitutes a time shift. Up-titration to the third dose level with predicted equivalent exposure to 600 µg b.i.d. in adults was assumed. A PK sampling scenario was evaluated, which considered trough samples on steady state of the first and second dose level and a PK profile (pre-dose and 1, 2, 4, 6, and 8 hours after dosing) on the third level. Although this scenario does not exactly mimic the planned sampling strategy, it is similar enough to generally assess parameter identifiability of the model.

Parameter identifiability was assessed based on a sample size of 25 subjects. When estimating all parameters (typical values and inter-individual variability [IIV]), the parameter correlation matrix showed high correlations between some parameters: k_{34} and k_m, V_m and k_{met}, k_{21} and V_m, k_{21} and k_{met}, CL and k_{21}, CL and V_m, and CL and k_{met}. Consequently, CL, k_{21}, V_m, and k_{met} have high estimation errors (> 400%). Since highly correlated parameters are mutually non-identifiable, it was decided to fix k_{21}, k_{met}, and k_{34}. The choice was based on the principle of not fixing parameters with body weight as covariate in the GRIPHON model.

Figure 1 Correlation of parameter estimates without body weight as covariate



Left: estimated correlation matrix of population parameters; right: estimated correlation matrix of inter individual variability.

14.7.2.2.2 Simulations

PK datasets (N 100) for pediatric patients were simulated based on the GRIPHON population PK model. Body weight ranges for each age cohort were derived from the 5th and 95th percentile of body weights observed in the corresponding age cohorts in registries of pediatric PAH patients [Table 2] [Ploegstra 2016]. Body weights were sampled from a beta distribution with shape factor 2. Starting and maximum allowed doses were defined based on the body weight as planned for the study [Table 3].

Table 2 Assumed body weight ranges by age cohort

Age cohort	*Body weight range*
≥ 2 to < 6 years	10 24 kg
≥ 6 to < 12 years	15 55 kg
≥ 12 to < 18 years	28 90 kg

Steady-state PK profile concentrations (pre-dose, 1, 2, 4, 6, 8, and 12 hours post-dose) were simulated for half of the patients within an age cohort at a low dose and for the other at a high dose. The low dose was the next dose level after the starting dose and the high dose

was the maximum allowed dose. In the study, steady-state profiles will be assessed at the starting dose and the individual maximum tolerated dose at Week 12. Hence, profiles will be obtained at a range of doses that is not pre-defined, but a result of the up-titration. However, since the PK is dose-proportional, a PK profile contains the same amount of information irrespective of the dose given (as long as the PK is in the quantifiable range of the PK assay). The simulated data was therefore considered representative of the data that will be generated in the study.

Table 3 Simulated doses for PK datasets

Body weight	*Starting dose*	*Low dose simulated*	*High dose simulated*
≥ 9 to < 25 kg	100 µg	200 µg	800 µg
≥ 25 to < 50 kg	150 µg	300 µg	1200 µg
≥ 50 kg	200 µg	400 µg	1600 µg

PK pharmacokinetic.

14.7.2.2.3 Parameter estimation and assessment of exposure estimation precision

To assess exposure estimation, precision evaluations of 3 scenarios have been performed, which are a first PK interim analysis including data from Cohort 1, a second PK interim analysis including data from Cohort 1 and Cohort 2, and a final analysis including data from all cohorts.

Based on simulated datasets for each scenario, model parameters were estimated and relative standard errors were obtained using standard pharmacometric software (Monolix). $AUC_{\tau,ss,combined}$ values were predicted by simulations with sampling from the parameter estimate covariance matrix. Subjects with body weights of 17, 35, and 59 kg were simulated 1000 times respectively to assess how well the $AUC_{\tau,ss,combined}$ can be predicted for patients with different body weights, i.e., ages. These body weights corresponded to the middle weight of the range assumed for each age category. The ratio of the 95th percentile to the median and of the median to the 5th percentile is reported as the $AUC_{\tau,ss,combined}$ prediction uncertainty.

As in the GRIPHON population PK model, body weight was included as covariate on CL, V_p, and V_m. In all estimations, k_{21}, k_{34}, and k_{met} were kept fixed to the GRIPHON parameter values. When estimating the IIV for all parameters, the IIV for V_p, k_{12}, k_{21}, V_m, k_{met}, k_{34}, and k_{43} tended to zero and were fixed at 10% in all estimations.

14.7.2.2.3.1 First and second PK interim analysis

The two PK interim analyses were evaluated using simulated PK data for Cohort 1 and for Cohort 1 and Cohort 2 respectively. Since drug absorption and metabolism is comparable to adults and the body weight ranges of both cohorts overlap with the range of patients in the GRIPHON study (i.e., 40 148 kg), it was considered acceptable to fix CL, V_m, and V_p to the values estimated based on the GRIPHON data. Nevertheless, the body weight effects on these parameters would be re-estimated during the first PK interim analysis. Using this estimation approach, parameters were estimated for the 100 simulated datasets.

For the first interim analysis, estimation errors for population parameters are limited (median RSEs below 50%), but are high for the covariate effects on CL, V_m, and V_p (median RSEs up to 100%) [Table 7]. Note that the analysis of this first PK analysis was performed with a different version of Monolix and using different analysis post-processing tools. This led to a different implementation of the IIV of T_{lag}, which was fixed in the new analysis. As T_{lag} has no impact on the $AUC_{\tau,ss,combined}$ this was judged acceptable.

For the second interim analysis, the median estimation error for the model parameters was not exceeding 60% and often below 30% [Table 8]. However, for some simulated datasets, the estimation errors were very high for the IIV on the absorption rate constant k_a and the elimination rate constant of the metabolite k_m and the effect of body weight on clearance CL.

Based on the parameter estimation uncertainty, the resulting uncertainty of $AUC_{\tau,ss,combined}$ predictions was assessed. For the first interim analysis only body weights of 35 and 59 kg were assessed as children in the first cohort have body weight considerably higher than 17 kg. Although estimation errors for some parameters were high, the uncertainty of the AUC prediction was well below 1.4-fold on average [Table 4]. At the second interim analysis, for children at body weights of 35 and 59 kg, the prediction uncertainty of $AUC_{\tau,ss,combined}$ was on average 1.2 1.3-fold across all simulated datasets [Table 5]. The uncertainty is higher for lower body weight, but still limited on average. The high estimation error for the body weight effect on the clearance is probably the reason why the maximal uncertainty for lower body weights is high (3.34 for a body weight of 17 kg).

Table 4 Prediction uncertainty of $AUC_{\tau,ss,combined}$ based on simulated data for children in Cohort 1 (≥ 12 to < 18 years)

Body weight (kg)	*$AUC_{\tau,ss,combined}$ prediction uncertainty (fold)*			
	median	mean	min	max
35	1.22	1.22	1.11	1.42
59	1.22	1.23	1.11	1.42

$AUC_{\tau,ss,combined}$ Combined exposure over one dosing interval at steady state.

Table 5 Prediction uncertainty of $AUC_{\tau,ss,combined}$ based on simulated data for children in Cohort 1 (≥ 12 to < 18 years) and Cohort 2 (≥ 6 to < 12 years)

Body weight (kg)	*$AUC_{\tau,ss,combined}$ prediction uncertainty (fold)*			
	median	mean	min	max
17	1.84	1.9	1.54	3.34
35	1.33	1.35	1.21	1.65
59	1.19	1.20	1.13	1.53

$AUC_{\tau,ss,combined}$ Combined exposure over one dosing interval at steady state.

14.7.2.2.3.2 Final PK analysis

In the final analysis, model parameters were estimated using the pooled data from all age cohorts. Compared to the second interim analysis, the youngest age cohort (≥ 1 to < 2 years) was added to the analysis dataset and all parameters besides the non-identifiable ones were estimated.

Parameters could be estimated well when pooling data from all age cohorts. The median estimation errors were < 45% for all parameters [Table 9]. For some simulated datasets, the estimation error for the IIV on K_m and the body weight effect on the clearance were high. The resulting $AUC_{\tau,ss,combined}$ prediction uncertainty was on average below 1.4-fold for subjects of 17, 35 and 59 kg [Table 6]. Although the body weight effect on the clearance had high estimation error in some runs, the maximal prediction uncertainty was only 1.6.

Table 6 Prediction uncertainty of $AUC_{\tau,ss,combined}$ based on simulated data for children ≥ 1 to < 18 years of age (Cohorts 1, 2, and 3)

Body weight (kg)	*$AUC_{\tau,ss,combined}$ prediction uncertainty (fold)*			
	median	mean	min	max
17	1.38	1.39	1.23	1.60
35	1.23	1.23	1.14	1.34
59	1.34	1.34	1.19	1.61

$AUC_{\tau,ss,combined}$ Combined exposure over one dosing interval at steady state.

14.7.3 DISCUSSION AND CONCLUSIONS

The sample size for a PK study in pediatric PAH patients was assessed based on two approaches. First, a number of subjects per age group was suggested considering exposure determination using NCA. Second, the suggested sample size was evaluated based on clinical trial simulations and model-based analysis as planned for dose selection/confirmation for the following Phase 3 study.

The first analysis suggested that 10 and 15 patients per age group are sufficient to determine the exposure up to a precision of a 2-fold and 1.75-fold difference respectively. Considering the rareness of pediatric PAH and that the final dose will be determined based on up-titration this sample size seems reasonable. It should also be noted that the main objective of the pediatric program is to demonstrate safety and efficacy of PAH treatment with selexipag in the Phase 3 study.

In the second analysis, the GRIPHON population PK model was used to perform clinical trial simulations for the planned pediatric study. PK parameters were re-estimated based on the simulated data. The prediction uncertainty for $AUC_{\tau,ss,combined}$ was used to evaluate with which precision the exposure can be predicted based on a model-based analysis of the PK data obtained from the PK study.

Two PK interim analyses in the study will be performed considering the PK data when all children older than 12 years (i.e., Cohort 1) and older than 6 years (i.e., Cohorts 1 and 2) concluded the study. According to the analysis described above, data from 15 patients in each cohort will provide a good estimate of the $AUC_{\tau,ss,combined}$ when accounting for the information in adults.

At the first interim analysis, it will allow for confirming the doses for Cohort 1 with 1.4-fold precision. However, as the modeling of simulated datasets showed high estimation errors

for some of the parameters depending on the acquired data quality, additional patients may need to be enrolled into Cohort 1.

The data at the second interim analysis are estimated to be sufficient for confirming the doses for Cohort 2 with approx. 1.4-fold precision and for Cohort 3 with approx. 2-fold precision.

For the final analysis, the data across all age cohorts will be pooled. All identifiable parameters will be estimated. Data from 10 patients from Cohort 3 ($\geq$ 2 to < 6 years) in addition to the 2 older age cohorts limit the fold change from the 95th percentile to median and the median to the 5th percentile to 1.4 on average.

The PK analyses performed during and after the study will also use the trough samples of intermediate dose levels, which were not considered in the sample size calculations.

The estimated uncertainty to determine the exposure is lower for the model-based analysis as compared to assessing the exposure by NCA. A sample size of 15 participants per age group as suggested by the first sample size assessment is, hence, reinforced based on clinical trial simulations. Data from the currently planned PK study with 40 participants in total will most likely provide a solid basis for staggered dose selection for each age cohort for the Phase 3 study.

At interim analyses, the sample size calculation will also be revised based on the obtained pediatric PK data and using adult data in a Bayesian approach. Confidence on the sample size calculation is increased at that stage as pediatric PK information will be available potentially giving the possibility to even reduce the sample size. As pediatric PAH is a rare disease, limiting the sample size is crucial for a feasible pediatric development program.

14.7.4 REFERENCES

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14.7.5 ADDITIONAL TABLES

Table 7 Relative standard error of parameter estimates based on simulated data for children ≥ 12 of age (Cohort 1)

Parameter	*Relative standard error (%)*			
	Mean	Median	Min	Max
T_{lag}	10.51	10.10	8.07	16.86
k_a	12.68	13.06	8.17	22.71
k_{12}	27.43	27.57	19.83	36.15
k_{43}	43.14	37.29	18.73	112.39
k_m	11.78	11.78	6.91	16.16
Body weight on CL	420.62	97.84	34.02	7280.03
Body weight on V_m	131.62	68.50	22.82	853.12
Body weight on V_p	103.53	66.18	19.64	473.75
ω(CL)	25.03	23.55	16.24	54.26
ω(k_a)	28.27	26.42	17.03	49.94
ω(k_m)	71.33	32.26	20.71	467.92
Proportional residual error selexipag	7.38	7.32	6.31	8.87
Proportional residual error ACT-333679	7.34	7.30	6.52	8.61

Table 8 Relative standard error of parameter estimates based on simulated data for children ≥ 6 of age (Cohorts 1 and 2)

Parameter	*Relative standard error (%)*			
	Mean	Median	Min	Max
T_{lag}	40.59	34.98	15.27	122.28
k_a	10.04	10.24	6.00	13.70
k_{12}	29.35	29.27	16.99	41.73
k_{43}	44.20	40.47	22.67	123.20
k_m	12.31	12.24	8.75	17.36
Body weight on CL	139.95	58.67	26.21	2742.56
Body weight on V_m	60.76	51.34	21.65	341.43
Body weight on V_p	54.83	47.80	22.86	224.99
ω(CL)	18.49	17.09	13.28	77.67
ω(k_a)	>1000	23.81	15.03	>1000
ω(k_m)	>1000	25.72	18.39	>1000
ω(T_{lag})	24.16	23.24	16.18	36.99
Proportional residual error selexipag	6.28	6.32	3.86	7.12
Proportional residual error ACT-333679	6.58	6.58	5.75	7.27

Table 9 Relative standard error of parameter estimates based on simulated data for children ≥ 2 to < 18 years of age (Cohorts 1, 2, and 3)

Parameter	*Relative standard error (%)*			
	Mean	Median	Min	Max
T_{lag}	38.31	34.20	17.17	149.85
k_a	8.98	9.06	6.19	11.26
CL	32.01	31.35	23.57	46.65
V_m	43.27	42.50	28.62	73.04
V_p	43.80	43.43	27.40	71.80
k_{12}	40.50	40.67	26.01	63.93
k_{43}	35.76	34.47	23.90	60.84
k_m	14.41	14.52	12.05	17.19
Body weight on CL	82.68	41.76	20.44	1417.01
Body weight on V_m	39.00	35.03	20.86	108.16
Body weight on V_p	33.69	31.94	19.72	78.48
ω(CL)	14.38	14.03	12.17	20.86
ω(k_a)	20.01	18.17	12.97	50.27
ω(k_m)	>1000	22.72	15.70	>1000
ω(T_{lag})	19.12	18.86	13.04	29.09
Proportional residual error selexipag	5.20	5.22	3.92	5.69
Proportional residual error ACT-333679	5.42	5.45	4.95	5.73

14.8 Appendix 8 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. A summary of previous amendments is provided below.

Amendment	Date	Main reason(s)
1	17 September 2018	Various clarifications on eligibility and discontinuation criteria, and corrections of mistakes.
2	1 March 2019	• Addition of the option to dispense 50 μg tablets only. • Addition of the systematic collection of signs and symptoms of right heart failure and events of disease progression. • Correction of mistakes.
3	6 May 2019	• Dispersion of tablets in water was prohibited. Only patients able to swallow tablets whole with water can be enrolled.
4	18 March 2020	• Additional treatment administration option with soft food. • Sample size increase in Cohort 3.
COVID-19 Appendix Version 1	16 June 2020	To provide a guidance on study conduct during the COVID-19 pandemic
5	05 October 2020	To reflect updates in safety reporting process.
6	19 May 2021	The main reason for the amendment was to add alternative options for administration of study intervention and implement other minor corrections.
COVID-19 Appendix Version 2	19 May 2021	To implement updates about 'Study conduct related to COVID-19 vaccine deployment for non-COVID-19 clinical trials' per Medicines and Healthcare products Regulatory Agency (MHRA) vaccination guidance.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceutical Ltd and Janssen Research and Development, a Division of Janssen Pharmaceutica NV

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	05-Oct-2021 15:58:12 (GMT)	Document Approval

Actelion Pharmaceuticals Ltd
Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

Protocol Title

A prospective, multicenter, open-label, single-arm, Phase 2 study to investigate the safety, tolerability and pharmacokinetics of selexipag in children with pulmonary arterial hypertension

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Protocol AC-065A203; Phase 2

JNJ-67896049 / ACT-293987 (selexipag)

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

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

EudraCT NUMBER: 2018-000145-39

Status: Approved
Date: 19 May 2021
Prepared by: Actelion Pharmaceuticals Ltd, a division of Janssen Research & Development
EDMS number: EDMS-RIM-263660, 5.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

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

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

GUIDANCE SPECIFIC TO THIS PROTOCOL

In relation to Protocol Section 4.3 (Inclusion criterion #7), urine pregnancy tests for females of childbearing potential may be shipped from the site to the subjects' home, in case a re-supply via site-visit is not possible.

In relation to Protocol Section 5.1.6 (Study treatment supply), for subjects unable to visit the clinic/hospital, direct-to-patient (DTP) shipment of study drugs may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP

shipments are deemed necessary, the process should be coordinated between the site and sponsor staff following the "COVID-19 DTP Guidance Document".

In relation to Protocol Section 12.3 "Informed Consent", consenting and re-consenting of subjects will be performed as applicable for the measures taken (including remote consenting by phone or video consultation) and according to local guidance for informed consent as applicable.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

- Study participants can undergo a COVID-19 vaccination procedure in compliance with applicable local governmental regulations.
- No pharmacokinetic interaction between the study intervention and currently available COVID-19 vaccines are expected. In addition, based on the mechanism of action of the study intervention and COVID-19 vaccines, no relevant interaction is expected.
- Any COVID-19 vaccine administered to a study participant is considered a concomitant medication and should be reported on the electronic case report form (eCRF).
- For serious adverse events (SAEs) reported after COVID-19 vaccination, the investigator should provide narrative details on the SAE form to allow adequate assessment of causality relationship between the reported SAE and vaccination. This is particularly relevant in cases where the reported SAE is an expected event with the study intervention and the COVID-19 vaccine. If the event is serious and considered to be related to both the COVID-19 vaccine and the study intervention, it is a serious adverse reaction and expectedness must be assessed. Suspected unexpected serious adverse reaction (SUSAR) reporting will be performed if the serious adverse reaction is unexpected as per applicable reference safety document.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-67896049 / ACT-293987 (selexipag) Clinical Protocol AC-065A203

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd, a division of Janssen Research & Development

Signature: PPD Date: PPD
(Day Month Year)

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

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Status: Approved, Date: 19 May 2021