Selexipag / ACT-293987

Pulmonary Arterial Hypertension

Protocol AC-065A303

GRIPHON OL

Long-term single-arm open-label study, to assess the safety and tolerability of selexipag (ACT-293987) in patients with pulmonary arterial hypertension

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Hereinafter called Actelion

Drug name / number

Selexipag / ACT-293987

Disease

Pulmonary arterial hypertension.

Protocol number and acronym

AC-065A303/GRIPHON OL

Long-term single-arm open-label study, to assess the safety and tolerability of selexipag (ACT-293987) in patients with pulmonary arterial hypertension

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Drug name / number

Selexipag / ACT-293987

Disease

Pulmonary arterial hypertension.

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Long-term single-arm open-label study, to assess the safety and tolerability of selexipag (ACT-293987) in patients with pulmonary arterial hypertension

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

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an independent ethics committee or institutional review board (IEC/IRB) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the subjects (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all subjects or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual subject. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

	Country	**Center number**	**Town**	**Date**	**Signature**
Center Principal Investigator					

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LIST OF ABBREVIATIONS

6MWD	6-minute walk distance
ACT-293987	Actelion's investigational drug selexipag, formerly known as NS-304
ACT-333679	The active metabolite of selexipag
AE	Adverse event
ALT	Alanine aminotransferase / serum glutamic pyruvic transaminase (SGPT)
AST	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase (SGOT)
ATC	Anatomic therapeutic chemical
AUC	Area under the concentration-time curve
b.i.d.	*Bis in diem* / twice a day
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CEC	Critical Event Committee
CRF	Case Report Form
CRO	Contract Research Organization
DP receptor	Prostaglandin D_2 receptor
dyn	Dyne (1 $g \cdot cm/s^2$)
EC	Ethics Committee
ECG	Electrocardiogram
EMEA	European Medicines Agency
EOS	End of study
EP receptor	Prostaglandin E receptor
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration
FP receptor	Prostaglandin F_2 receptor
GCP	Good Clinical Practice
GPCR	G-protein coupled receptor

GRIPHON	Prostacyclin (PGI_2) Receptor agonist In Pulmonary arterial HypertensiON
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IP receptor	Prostacyclin receptor, PGI_2 receptor
IPAH	Idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board
i.v.	Intravenous
MLA	Marked laboratory abnormality
mPAP	Mean pulmonary arterial pressure
NDA	New drug application
NS-304	Original Nippon Shinyaku name of selexipag
NYHA	New York Heart Association
OL	Open-label
p.o.	*Per os* / orally
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic(s)
PDE-5	Phosphodiesterase type-5
PGI_2	Prostacyclin (Prostaglandin I_2)
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RVH	Right ventricular hypertrophy

RVSP	Right ventricular systolic pressure
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Systemic vascular resistance
$t_{½}$	Elimination half-life
t_{max}	Time to maximum plasma concentration
TP receptor	Thromboxane A_2 (TXA_2) receptor
TXA_2	Thromboxane A_2
ULN	Upper limit of normal
UV	Ultraviolet
WHO	World Health Organization

SUBSTANTIAL GLOBAL AMENDMENT 8

Amendment rationale

This amendment applies to global protocol AC-065A303 version 8, dated 30 June 2017. The resulting amended global protocol is version 9, dated 6 February 2019.

The main reason for this amendment is to include guidance for concomitant administration of selexipag and moderate inhibitors of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide) as described in the current Investigator's Brochure (IB) Version 13 [Selexipag IB].

Results of the completed Phase 1 study AC-065-117 showed that concomitant administration of selexipag (200 µg b.i.d.) with clopidogrel (300 mg as a loading dose or maintenance dose of 75 mg once daily), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite by approximately 2.2-fold and 2.7-fold following loading dose and maintenance dose, respectively. If a moderate inhibitor of CYP2C8 is concomitantly administered with selexipag, the dosing frequency of selexipag should be reduced to once daily (resulting in halving of the daily dose) unless, based on medical judgment, continuation of b.i.d. therapy is indicated. Dosing frequency of selexipag should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped.

Clinical information [Section 1.3.2] has been updated to include reference to the recently completed studies. Results of these studies are summarized in the current Selexipag IB.

The statistical analysis section has been updated according to ICH E6.

The data collection section is updated to allow the use of a standard ballpoint pen to complete the Case Report Forms (CRF).

Sponsor and CRO contact details have been updated.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document, showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The main sections of the protocol affected by this amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis.

1.3.2.1 Phase 1 studies in healthy subjects
1.3.2.2 Phase 2 studies in patients with pulmonary arterial hypertension
3.2.4.1 Allowed concomitant medications
5 Statistical Methodology and Analyses.
6.1.3.1 Data collection
7 References

Summary of previous amendments

Amendment	Date	Main reason(s)
7	30 June 2017	• To add contraindication of strong CYP2C8 inhibitors such as gemfibrozil in accordance to IB Version 11 (Amendment 2) • To add information on the lack of studies to determine the effect of moderate inhibitors of CYP2C8, and strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite.
6	25 January 2017	• Further to new drug-drug interaction study results: – concomitant administration of strong CYP2C8 inhibitors such as gemfibrozil should be avoided. – in case of concomitant administration of rifampicin, dose adjustment of selexipag may be required.
5	15 June 2016	• Disbandment of the Data Monitoring Committee involved in the AC-065A302 (GRIPHON) study as of 1 July 2016. • Disbandment of the Ophthalmology Safety Board as of 1 July 2016. • In the protocol, the reference to the selexipag IB section 6 was replaced with the complete list of AEs.
4	16 March 2015	• The possibility to up-titrate selexipag at unscheduled visits (for patients who have not reached the maximum allowed dose) was introduced. • The overall duration of the AC-065A303 (GRIPHON OL)

		study was changed from "until the approval of selexipag in PAH" to "until selexipag is commercially available". • Temporary concomitant use of selexipag and intravenous (i.v.), subcutaneous (s.c.), or inhaled prostacyclin and prostacyclin analogs was now allowed when deemed medically indicated for the patient. • A discontinuation criterion for patients diagnosed with pulmonary veno-occlusive disease (PVOD) was introduced. • The Informed Consent Form (ICF) was updated with safety and efficacy information from the pivotal GRIPHON study.
3	19 April 2013	• Sample size was increased from 670 to 1150. • Collection of safety data in the clinical database was extended to vital signs, body weight, concomitant medications, and laboratory results. • Guidance for management of patients with liver impairment was provided. • Eligibility of GRIPHON patients to GRIPHON OL was extended to patients with worsening of PAH during the Treatment Extension period of the GRIPHON study. • It was clarified that GRIPHON OL results will be reported in combination with the GRIPHON study results. • The core ICF was updated to include the definition of reliable methods of contraception consistent with the definition already used for the same patients in the GRIPHON study. • Considering the protocol Amendment 6 of the GRIPHON study, GRIPHON OL could no longer be considered a stand-alone study. Consequently, the statistical section was shortened.
2	20 December 2010	• The precautionary wording regarding sun exposure was removed. • The independent Data Monitoring Committee reviewing unblinded safety data of GRIPHON was also assigned the review of safety data from the GRIPHON OL study.
1	19 March 2010	• Further to the merge of the double-blind studies AC-065A301 and AC-065A302 into one single study, all references to these 2 studies in the protocol AC-065A303 (GRIPHON OL) were removed and replaced by the reference to the merged

	protocol AC-065A302 (GRIPHON). • Patients who experienced a CEC-confirmed clinical worsening event during GRIPHON study could only enter GRIPHON OL study after their GRIPHON Week 16 visit and after written approval from the Sponsor. These restrictions were removed. • A time limit of 2 weeks after the last visit in GRIPHON was introduced for entering the GRIPHON OL study. • Clarification that prostacyclin and prostanoid therapy were prohibited not only during the GRIPHON OL study but also in the transition period between GRIPHON and GRIPHON OL. • Additional telephone calls alternating with the scheduled visits were introduced. • The text of the core patient information was updated to reflect the changes in the protocol described above. In addition to these changes, the risk and discomfort section was updated to include information on nonclinical study signals regarding intussusception, changes in the bone structure, and inhibition of platelet aggregation.

PROTOCOL SYNOPSIS AC-065A303/GRIPHON OL

TITLE	Long-term, single-arm, open-label study, to assess the safety and tolerability of selexipag (ACT-293987) in patients with pulmonary arterial hypertension
ACRONYM	GRIPHON OL: Prostacyclin (P**G**I_2) **R**eceptor agonist **I**n **P**ulmonary arterial **H**ypertensi**ON** **O**pen **L**abel.
OBJECTIVES	To assess the long-term safety and tolerability of selexipag in patients with pulmonary arterial hypertension (PAH).
DESIGN / PHASE	Multicenter, open-label (OL) extension, single-arm, Phase 3 study.
STUDY PLANNED DURATION	**First patient First visit** 07Jul2010 **Last patient First visit** open **Last patient Last visit** open
CENTER(S) / COUNTRY(IES)	190 centers in 44 countries (planned).
PATIENTS / GROUPS	Up to 1150 patients
INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any study-mandated procedure. 2. Patients who have completed the double-blind study AC-065A302 as scheduled per protocol (i.e., treated until unblinding of the study), *or* Patients who have experienced a morbidity event (confirmed by the Critical Event Committee [CEC]) during study AC-065A302, *or* Patients experiencing a worsening of PAH during the Treatment Extension period of AC-065A302 and for whom a written approval to roll over into this study has been obtained from the sponsor. 3. Women of child-bearing potential[1] included in study AC-065A303 must use a reliable method of contraception

[1] A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

	(with a failure rate of less than 1% per year) until one month after study drug discontinuation.
EXCLUSION CRITERIA	1. Pediatric patients (i.e., < 18 years of age). 2. Patients who are not able to perform the Visit 1 of AC-065A303/GRIPHON OL within 2 weeks (i.e., 14 days) of the last visit in AC-065A302/GRIPHON. 3. Patients who have started receiving prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) since the last study drug intake in AC-065A302/GRIPHON[2]. 4. Severe hepatic impairment (Child-Pugh C). 5. Females who are pregnant or plan to become pregnant during the study, or are breastfeeding. 6. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence, or psychiatric disease. 7. Known hypersensitivity to selexipag or any of the excipients.
CONCOMITANT MEDICATIONS	**Allowed** • Endothelin receptor antagonists (ERAs), phosphodiesterase type-5 (PDE-5) inhibitors, and/or riociguat are permitted for the treatment of PAH. • Inhaled, i.v., and s.c. prostacyclin and prostacyclin analogs (i.e., epoprostenol, treprostinil, iloprost) are permitted as deemed medically indicated by the Investigator. • Single administration of intravenous [i.v.]/inhaled prostacyclin and analogs used for acute vasodilator testing during a right heart catheterization (RHC) procedure is

- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years with amenorrhea for at least 24 consecutive months prior to screening

[2] Single administration of i.v./inhaled prostacyclin or analogs used for acute vasodilator testing during a RHC procedure is allowed.

	allowed. • Treatment with moderate inhibitors of CYP2C8 is allowed. If a moderate inhibitor of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide) is concomitantly administered with selexipag, the dosing frequency of selexipag should be reduced to once daily (resulting in halving of the daily dose) unless, based on medical judgment, continuation of twice daily (b.i.d.) therapy is indicated. Dosing frequency of selexipag should be reverted to b.i.d. when co-administration of moderate CYP2C8 inhibitor is stopped. • If rifampicin is administered concomitantly with selexipag, dose adjustment of selexipag may be required. **Prohibited** • Oral IP-receptor agonists (e.g., beraprost, treprostinil) are prohibited from the last study drug intake in AC-065A302/GRIPHON until end of study (EOS) in AC-065A303/GRIPHON OL. • Concomitant use of strong inhibitors of CYP2C8 such as gemfibrozil until EOS in AC-065A303/GRIPHON OL. • Any investigational drug other than selexipag.
STUDY PERIODS	**<u>Titration period:</u>** • For patients randomized to placebo in AC-065A302 who completed the double-blind study as scheduled per protocol (i.e., treated until unblinding of the study). • For patients who experienced a morbidity event (confirmed by the CEC) in the study AC-065A302. • For patients enrolled with a written approval from the sponsor after experiencing a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON. These patients' dose will be up-titrated starting from 200 µg b.i.d. in increments of 200 µg b.i.d. until their individual highest tolerated dose is reached, independently of the treatment arm they were allocated to during the study AC-065A302. **<u>Maintenance period</u>:** • For patients randomized to active treatment in AC-065A302 who completed the double-blind study as scheduled per protocol (i.e., treated until unblinding of the study) and for all

	patients who completed the titration period in this OL study. Study treatment for each patient lasts from his/her Visit 1 date until the end of the trial i.e., until whichever of the following occurs first: (i) selexipag is commercially available in this indication in the patient's country, (ii) the sponsor decides to stop study AC-065A303/GRIPHON OL, or (iii) the patient, or the investigator decide to discontinue study drug. **Post-treatment safety follow-up**: 30 days after study drug discontinuation. **End of Study:** The overall study is considered completed when all patients have completed their individual safety follow-up phone call or have died, withdrawn consent or have been lost to follow-up.
INVESTIGATIONAL DRUG	Tablets of 200 µg selexipag for oral administration Depending on the highest tolerated dose of the patient, a single dose will consist of 1 to 8 tablets (200 µg to 1600 µg) b.i.d. Any interruption of study drug intake of 3 days or more will require a new up-titration. Patients who were on placebo, experienced a confirmed morbidity event during study AC-065A302/GRIPHON, or for whom written approval has been obtained from sponsor after a PAH worsening during the AC-065A302/GRIPHON Treatment Extension period will enter the titration period. Patients coming from study AC-065A302/GRIPHON already taking selexipag will continue on the same dose. During the maintenance period, the dose of patients who did not reach the maximum of 1600 µg b.i.d, can be up-titrated based on the investigators' medical judgment, only after a site visit (scheduled or unscheduled) and in increments of 200 µg b.i.d. each time. Re-uptitrations to a previously reached dose can be done based on phone calls and do not need site visits. The dose can be reduced at any time if the investigator identifies a tolerability concern for a patient. **Study drug discontinuation:** If the investigator becomes aware that a patient has developed

	moderate hepatic impairment (e.g., Child-Pugh B) at any time during the AC-065A302/GRIPHON or the AC-065A303 /GRIPHON OL study, then it is the responsibility of the investigator to evaluate the benefit-risk of keeping the patient on study drug. In case a patient has developed severe hepatic impairment (e.g., Child-Pugh C), the study drug must be discontinued. Should signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. If confirmed, selexipag must be discontinued.
COMPARATOR DRUG	NA
TOLERABILITY / SAFETY ENDPOINTS	• Treatment-emergent AEs up to 3 days after study drug discontinuation. • Treatment-emergent SAEs up to 3 days after study drug discontinuation. • AEs leading to permanent discontinuation of study drug.
STATISTICAL METHODOLOGY	This study will be analyzed using data from both AC-065A302/GRIPHON and AC-065A303/GRIPHON OL databases. A statistical analysis plan (SAP) will be written and finalized before database lock of the AC-065A303/GRIPHON OL study. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivation.
STUDY COMMITTEES	The Steering Committee involved in the study AC-065A302/GRIPHON will provide guidance on the conduct of the study. The Data Monitoring Committee involved in the study AC-065A302/GRIPHON will also review safety data from this study up to 1 July 2016 (date of disbandment of the committee). An Ophthalmology safety board will be consulted up to 1 July 2016 (date of disbandment of the board) for their opinion and recommendation in case of specific ophthalmological findings.

Table 1 Visit and Assessment Schedule for patients who need to up-titrate their dose

		TITRATION PERIOD[1]										**MAINTENANCE PERIOD**			
	Visit[2] **1**	Tel.[4] W1	Tel[4] W2	Tel[4] W3	**Visit 2**	Tel[4] W5	Tel[4] W6	Tel[4] W7	**Visit 3**	Tel[4] W12	**Visit 4**	**Visit 5**	Tel[4]	**EOS Visit**	**Safety follow up**[4]
	Day 1	Day 8 ± 3 days	Day 15 ± 3 days	Day 22 ± 3 days	**Week 4** ± 3 days	Week 5 ± 3 days	Week 6 ± 3 days	Week 7 ± 3 days	**Week 8** ± 3 day	Week 12 ± 3 days	**Week 16** ± 3 days	**Month 6* and every 6 months** ± 7 days	Month 9 and every 6 months ± 7 days		30 to 37 days after EOT
Written informed consent[7]	X														
Concomitant medications	X				X				X		X	X		X	
Vital signs	X				X				X		X	X		X	
Body weight	X				X				X		X	X		X	
Laboratory tests[5]	X				X				X		X	X		X	
Physical examination[6]	X				X				X		X	X		X	
Pregnancy test (if appl.)[3]	X				X				X	X	X	X	X	X	X
Dispensing of study drug	X				X				X		X	X			
Drug accountability					X				X		X	X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Only for patients who were on placebo, patients who experienced a confirmed morbidity event during AC-065A302/GRIPHON, or patients experiencing a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON and for whom a written approval to roll over into this study has been obtained from the sponsor; [2] Visit 1 should correspond to the last visit in the double-blind study or, if not possible, must be within 2 weeks (14 days). When Visit 1 is performed on the same day as the last visit of the double-blind study, assessments that are common to both studies are not to be repeated. Results are to be reported on CRF pages of both studies; [3] Monthly urine (or serum) pregnancy test for women of childbearing potential until 1 month after study drug discontinuation; [4] Scheduled telephone call; [5] Hematology and blood chemistry tests to be performed at Visit 1 only if the last assessment in AC-065A302/GRIPHON was performed more than 4 weeks before, and then at every visit until EOS. [6] Physical examination results will not be collected in the CRF but clinically relevant changes from baseline must be reported as adverse events. [7] Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available.
* 6 months correspond to 26 weeks.
CRF = Case Report Form; EOS = End of Study; EOT = End of Treatment.

Table 2 Visit and Assessment Schedule for patients treated with selexipag in the GRIPHON study

		TITRATION PERIOD[2]	**MAINTENANCE PERIOD**				
	Visit[1] 1	NA	Tel[4] W12	**Visit 5**	Tel[4]	**EOS Visit**	**Safety follow up[4]**
	Day 1	NA	Week 12 ± 3 days	**Month 6* and every 6 months** ± 7 days	Month 9 and every 6 months ± 7 days		30 to 37 days after EOT
Written informed consent[7]	X						
Concomitant medications	X	NA		X		X	
Vital signs	X	NA		X		X	
Body weight	X	NA		X		X	
Laboratory tests[5]	X	NA		X		X	
Physical examination[6]	X	NA		X		X	
Pregnancy test (if appl.)[3]	X	NA	X	X	X	X	X
Dispensing of study drug	X	NA		X			
Drug accountability		NA		X		X	
Adverse events	X	NA	X	X	X	X	
Serious adverse events	X	NA	X	X	X	X	X

[1] For patients on study treatment until unblinding of AC-065A302/GRIPHON, Visit 1 should correspond to the last visit in the double-blind study AC-065A302/GRIPHON or, if not possible, must be within 2 weeks (14 days); [2] Not applicable, patient will switch directly from Visit 1 to Week 12 phone call and Visit 5; [3] Monthly urine (or serum) pregnancy test for women of childbearing potential until 1 month after study drug discontinuation; [4] Scheduled telephone call. [5] Hematology and blood chemistry tests to be performed at Visit 1 only if the last assessment in AC-065A302/GRIPHON was performed more than 4 weeks before, and then at every visit until EOS. [6] Physical examination results will not be collected in the CRF but clinically relevant changes from baseline must be reported as adverse events. [7] Throughout the course of the study, it is recommended to regularly discuss with the patient whether new PAH therapy is becoming available.

* 6 months correspond to 26 weeks.

CRF = Case Report Form; EOS = End of Study; EOT = End of Treatment; NA = Not applicable.

1 BACKGROUND AND RATIONALE

1.1 Pulmonary arterial hypertension

The most serious chronic disorder of the pulmonary circulation is pulmonary arterial hypertension (PAH). PAH is characterized by pulmonary arterial vasoconstriction and vascular remodeling resulting in a progressive increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately leading to right ventricular failure and death. PAH is defined as a sustained elevation of mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest (or > 30 mmHg with exercise), with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and PVR > 3 Wood units (> 240 dyn s cm^{-5}) [Rubin 2004].

The Updated Clinical Classification of Pulmonary Hypertension [Simonneau 2009] classifies the numerous conditions that are known to lead to, or to be associated with, the development of PAH into five groups, based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach. PAH may occur in the absence of a demonstrable cause (idiopathic or heritable), as the result of the use of drugs and toxins, or as a complication of congenital heart disease, systemic conditions such as connective tissue disease, particularly scleroderma, HIV infection, portal hypertension, schistosomiasis, or chronic hemolytic anemia.

The pathophysiology of PAH involves multiple pathways, which are influenced by many overlapping secondary messenger systems. Vasoconstriction, obstructive remodeling of the pulmonary vessel wall caused by extensive cell proliferation and reduced rates of apoptosis, inflammation, and thrombosis within the pulmonary arteries are promoted by activation of these pathways, and lead to elevated PAP and PVR, and eventually right ventricular failure.

Currently, there is no cure for PAH. However, improved understanding of the pathogenic factors of the disease has led to the development of new therapies targeting specific pathways (the prostacyclin pathway; the endothelin pathway; and the nitric oxide pathway) [Humbert 2004, Farber 2004] that are believed to play an important role in the pathogenesis of PAH.

Today, a total of seven agents are currently approved for the treatment of PAH in the United States and/or in Europe: intravenous prostacyclin (epoprostenol), other prostanoid analogs, i.e., treprostinil (intravenous [i.v.], subcutaneous [s.c.] and inhaled), and iloprost (inhaled), endothelin receptor antagonists (ERAs; bosentan, ambrisentan) and phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil, tadalafil). All of these agents have been shown to improve exercise capacity as assessed by 6-minute walk test in short-term randomized placebo-controlled trials.

Pure vasodilators, such as calcium channel blockers, are effective only in a minority of patients who have an acute response to vasodilator testing [Rich 1992, Sitbon 2005].

The available therapies have positive effects in PAH, but in many patients the disease will progress and PAH remains a serious life-threatening condition.

Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

Before the development of recent therapeutic options, idiopathic PAH (IPAH) was rapidly progressive and led to right heart failure and death. In the early 1990s, it was reported that the median survival of patients was 2.8 years after diagnosis [D'Alonzo 1991]. The first large prospective studies showed an actuarial survival rate of 68 to 77%, 40 to 56%, and 22 to 38% at one, three, and five years, respectively [D'Alonzo 1991, Galiè 2009].

1.2 Prostacyclin and pulmonary hypertension

Prostacyclin (Prostaglandin I_2 / PGI_2), a metabolite of arachidonic acid, is formed via the cyclooxygenase pathway. Endothelial cells are the main source of PGI_2 and its action is directed to both the local vascular wall and to blood cells, particularly those that adhere to the endothelium. It is a potent endogenous vasodilator, inhibitor of platelet aggregation and smooth muscle cell proliferation through its activity at the prostacyclin (IP) receptor [O'Grady 1980].

The IP receptor is a G protein-coupled receptor (GPCR) that activates adenylate cyclase, leading to increased cyclic adenosine monophosphate (cAMP) levels in the target cells. cAMP has been widely implicated in the control of pulmonary vascular tone and inhibition of mitogenic pathways in vascular smooth muscle cells.

Patients with PAH have been shown to have a deficiency of PGI_2 [Christman 1998] and of PGI_2 synthase [Tuder 1999] causing an imbalance in PGI_2 and thromboxane A_2 (TXA_2), its physiological antagonist. These findings led to the rationale that targeting the PGI_2 pathway with IP receptor agonists could be beneficial.

The first, epoprostenol, the chemical analog of PGI_2, was approved in 1996 for NYHA/WHO functional class III-IV IPAH and PAH associated with scleroderma, and was shown to improve exercise tolerance and survival in patients with IPAH [Barst 1996]. Since continuous intravenous epoprostenol became available, the prognosis for patients suffering from PAH has significantly improved. However, due to its short half-life and chemical instability, long-term epoprostenol therapy requires a permanently implanted central venous catheter and a portable infusion pump, exposing patients to a series of complications including catheter-related embolism or thrombosis, infection, and delivery system malfunctions resulting in poorly tolerated overdosing or underdosing.

The complexity of epoprostenol therapy has led to attempts to develop other prostanoids with simpler modes of delivery. Treprostinil, a stable PGI_2 analog with a half-life of 3 h, has been developed for intravenous, subcutaneous delivery, and inhalation. It has beneficial effects on exercise and hemodynamics, which depend on the dose achieved. This, in turn, is determined by the patient's ability to tolerate the drug's side effects. Iloprost, another PGI_2 analog, has been approved for intravenous delivery and inhalation. Inhaled iloprost shows some selectivity of the hemodynamic effects to the lung vasculature, thus reducing systemic side effects, but has to be inhaled between 6 to 9 times per day, which may limit compliance.

The inconveniences of the administration routes of the above-mentioned drugs, such as injection site pain and reaction (redness and swelling) for subcutaneous administrations, or line infections, sepsis, hematoma, and local pain for intravenous infusions, are another factor influencing the patient's benefit from these treatments.

1.3 Selexipag – a non-prostanoid IP receptor agonist

Selexipag is an orally available drug that is readily hydrolyzed to the active metabolite ACT-333679. Both selexipag and ACT-333679 are potent and selective agonists at the human IP receptor.

ACT-333679 has a 13-fold higher affinity for the human IP receptor [Selexipag IB] and is 15-fold more potent than selexipag in activating the human IP receptor. *In vitro* studies showed that ACT-333679 has at least 130-fold lower affinity for other human prostanoid receptors such as the prostaglandin $E_{1–4}$, D_2, and F_2 receptors, as well as the TXA_2.

Selexipag has been selected for further clinical development based on its pharmacokinetic (PK) profile observed in Phase 1 studies and the results from the Phase 2 study [Section 1.3.2].

1.3.1 Preclinical information

In vivo pharmacology studies demonstrated that orally administered selexipag significantly reduced right ventricular systolic pressure (RVSP) and right ventricular hypertrophy (RVH) in a rat model of PAH. Selexipag also ameliorated the impaired relaxant response of the pulmonary artery from these animals.

Furthermore, selexipag significantly increased survival of rats with monocrotaline-induced PAH [Kuwano 2008].

In normotensive rats prolonged administration of selexipag did not attenuate the acute increase in femoral skin blood flow induced by the compound, suggesting lack of desensitization of the IP receptor [Kuwano 2007].

1.3.2 Clinical information

1.3.2.1 Phase 1 studies in healthy subjects

During the Phase 1 program selexipag was well tolerated after single and multiple daily oral doses of up to and including 1600 µg b.i.d. No serious adverse events (SAEs) were reported in any of the Phase 1 studies and the majority of the adverse events (AEs) were of mild intensity. The most frequently reported AEs were headache, myalgia, jaw pain, dizziness, nausea, vomiting, arthralgia, diarrhea, and abdominal pain. No clear dose relationship could be established for the above-mentioned AEs.

Multiple doses of selexipag up to 1600 µg b.i.d. (study AC-065-101), starting with 400 µg b.i.d. and up-titrated in increments of 200 µg every 3rd day, were well tolerated. Most AEs were mild or moderate in intensity. The incidence of AEs was similar for all treatment groups, which suggests improved tolerability after repeated dosing. Tolerability decreased at a dose of 1800 µg selexipag b.i.d. and led to an increase in moderate AEs (headache, myalgia, and nausea) that required concomitant medication. The maximum dose tested in Japanese subjects was 600 µg b.i.d. There were no consistent differences in the number and type of AEs with increasing dose of selexipag.

Treatment with selexipag up-titrated in increments of 200 µg to 1800 µg (the highest dose tested in Caucasian subjects) or 600 µg (the highest dose tested in Japanese subjects) (study AC-065-101 and NS304/P1/01), were not associated with clinically relevant changes in systolic and diastolic blood pressures, heart rate, electrocardiogram (ECG) intervals and morphology, vital signs and laboratory tests. In addition, in the AC-065-101 study, no changes were observed in thyroid markers, orthostatic hypotension, platelet aggregation test, bone formation, bone resorption markers, and coagulation markers.

Plasma concentration-time profiles and PK parameters of selexipag and ACT-333679 were comparable across the studies performed in healthy subjects. The plasma concentration-time profiles of selexipag revealed that, in general, maximum plasma concentrations were achieved in about 1–2 h after single-dose and multiple-dose administration. Thereafter, plasma concentrations of selexipag decreased quickly. The plasma concentration-time profiles of ACT-333679 showed that, in general, maximum plasma concentrations were achieved in about 3–4 h after single- and multiple-dose administration. Thereafter, plasma concentrations of ACT-333679 compared to selexipag decreased more slowly. In the study AC-065-101 the exposure (area under the concentration-time curve [AUC]) to ACT-333679 is approximately four times higher than to selexipag.

Following multiple oral administrations of selexipag, the apparent elimination half-lives of selexipag and its active metabolite ACT-333679 were between 0.9 and 1.9 hours and

between 7.9–14.5 h, respectively, which supports twice daily oral administration. The PK of selexipag, after both single- and multiple-dose administration, were approximately dose-proportional over the tested dose range, i.e., up to a single dose of 800 µg and multiple doses of 1800 µg b.i.d. of selexipag. After multiple-dose administration, steady-state conditions of selexipag and ACT-333679 were reached on Day 3. No relevant accumulation in plasma either of selexipag or ACT-333679 occurred after multiple-dose administrations.

Results from study QGUY/2006/NS304/-01 indicate that food intake delayed the exposure to ACT-333679, as the median t_{max} increased from 2.5 hours during fasting to 4 hours in fed state, and decreased the exposure to ACT-333679 by 27%.

More subjects reported AEs in the fasted period than in the fed period. These results may indicate better tolerability of selexipag when administered with food.

Selexipag did not influence the PK or pharmacodynamics (PD) of warfarin. Similarly, co-administration of warfarin with selexipag did not have an impact on the exposure to selexipag or its active metabolite ACT-333679.

The metabolism and excretion of selexipag were studied following a single dose administration of radioactively labeled ACT-293987A (400 µg) (study 186933). 105% of the radioactivity was excreted primarily via feces (93%) and urine (12%). Excretion was complete after 5 days indicating no relevant retention of drug-related material in man.

When comparing the PK of selexipag and ACT-333679 from study QGUY/2006/NS30/-01, which mainly included Caucasian subjects, to those of study NS304/P1/01, which included only Japanese subjects, the concentrations of both selexipag and ACT-333679 were higher in Japanese subjects. The difference in the PK was mainly due to the difference in body weight. When corrected for body weight a small residual difference was observed, however this difference was within one standard deviation of the mean and not consistent between the different dose levels. The clinical relevance of this observation is currently unknown.

In study AC-065-102, investigating the photosensitizing potential of selexipag, doses of 800 and 1200 µg selexipag did not show any difference in the phototoxic index compared to placebo and the mild photosensitizing agent ciprofloxacin. The study did not indicate that selexipag has clinically relevant photosensitizing potential in humans.

Results of study AC-065-113 (Part I) showed that in the presence of multiple-dose gemfibrozil (600 mg b.i.d.), a strong CYP2C8 inhibitor, a 2-fold increase in selexipag exposure and 11-fold increase in ACT-333679 exposure was observed.

Results of study AC-065-113 (Part II) showed that concomitant administration of selexipag and multiple-dose rifampicin (600 mg once daily; a moderate inducer of CYP2C8) led to no relevant change in exposure to selexipag in terms of AUC, while exposure to the active metabolite in terms of AUC decreased by half.

Results of study AC-065-117 showed that concomitant administration of selexipag (200 µg b.i.d.) with clopidogrel (300 mg as a loading dose or maintenance doses of 75 mg once daily), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite by approximately 2.2-fold and 2.7-fold following loading dose and maintenance dose, respectively.

The effects of strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite have not been studied. Concomitant administration may result in a significant increase in exposure to selexipag or its active metabolite.

Results of the completed Phase 1 studies are described in the current version of the Investigator's Brochure [Selexipag IB].

1.3.2.2 Phase 2 studies in patients with pulmonary arterial hypertension

A Phase 2a proof-of-concept study in PAH (NS-304/-02) was completed in July 2009. Study NS-304/-02 was conducted in seven European centers and enrolled 43 patients with PAH, who were randomized in a 3:1 ratio to selexipag (n = 33) or placebo (n = 10). All enrolled patients received double-blind study treatment, which was prematurely discontinued in three patients (two on selexipag and one on placebo). Median exposure to study treatment was 146 days in the placebo group and 149 days in the selexipag group. For most patients, PAH was idiopathic (70% and 73% of patients in the placebo and selexipag groups, respectively). At baseline, all patients were receiving either an ERA (bosentan, 70% and 61% of patients in the placebo and the selexipag group, respectively, or sitaxentan in four patients in the selexipag group only) or a PDE-5 inhibitor (sildenafil 60% and 64% of patients in the placebo and the selexipag group, respectively). Three patients in the placebo group (30%) and 12 patients in the selexipag (36%) were receiving both an ERA and a PDE-5 inhibitor.

After 17 weeks of treatment, mean PVR was decreased from baseline in the selexipag group (−168 ± 45 dyn·sec/cm^5) and increased in the placebo group (137 ± 35 dyn·sec/cm^5). Values at Week 17 expressed as a percent of baseline values showed a significant 30.3% reduction in PVR with selexipag compared with placebo (P = 0.0045, Wilcoxon rank sum test). Similar improvements in PVR were observed in the all randomized analysis set.

After 17 weeks of treatment, the mean 6-minute walk distance (6MWD) increased from baseline in the selexipag group (+24.7 ± 12.9 meters) and was unchanged in the placebo group (+0.4 ± 8.9 meters), which resulted in a mean treatment effect of 24.2 ± 23.7 meters (P = 0.2218, Wilcoxon rank sum test). Three subjects showed aggravation of PAH during the double-blind study, two patients in the placebo group (20%) and one (3.3%) patient in the selexipag group. All three patients were in NYHA/WHO functional class III at baseline. A statistically significant increase of Cardiac Index was observed in the selexipag group when compared to a decrease in the placebo group, which resulted in a mean treatment effect: 0.48 ± 0.17 L/min/m^2, (± standard error) (P = 0.0137, Wilcoxon rank sum test). A statistically significant decrease of systolic vascular resistance (SVR) was observed in the selexipag group when compared to an increase in the placebo group, which resulted in a mean treatment effect: –407.8 ± 164.2 dyn·sec/cm^5, (± standard error) (P = 0.0071, Wilcoxon rank sum test).

Ten (100%) patients in the placebo group reported a total of 39 treatment emergent-adverse events, whilst 31 (93.9%) patients in the selexipag group reported a total of 182 adverse events (AE). The most frequently reported AE in the active group was headache, reported in 22 (66.7%) patients in the selexipag compared to two (20%) patients in the placebo group. In the selexipag group, pain in jaw, pain in extremity, nausea, diarrhea, flushing, dizziness, cough and myalgia were reported in 12 patients (36.4%), 10 patients (30.3%), nine patients (27.3%), six patients (18.2%), six patients (18.2%), five patients (15.2%), four patients (12.1%) and four patients (12.1%), respectively. Most AEs in both treatment groups were of mild or moderate intensity, but a severe event was experienced by a larger proportion of patients on placebo (40%) than in the selexipag group (18.2%). Seven SAEs were reported in four patients (40%) in the placebo group. Fourteen SAEs were reported in six patients (18.2%) in the selexipag group. There were no changes from baseline to the end of treatment in either systolic or diastolic blood pressure, or in pulse rate in the placebo group and in the selexipag group. The analysis of marked laboratory abnormalities (MLA) in the selexipag compared to the placebo group did not reveal any relevant increase of the incidence of MLA after selexipag treatment. No clinically relevant ECG changes were observed in either treatment group.

Results of completed studies are described in the current version of the IB [Selexipag IB].

1.4 Study rationale

1.4.1 Medical and regulatory background

Selexipag is a new, selective, orally active non-prostanoid IP receptor agonist selected for clinical development in PAH.

Prostacyclin (epoprostenol) and analogs like treprostinil (intravenous, subcutaneous, and inhaled) and iloprost (inhaled) have been approved for the treatment of PAH. However, the administration routes are not always convenient. For subcutaneous administrations, injection site pain and reaction (redness and swelling) occur in the majority of patients. For intravenous infusions, line infections, sepsis, hematoma, and local pain are most common. Inhaled iloprost has to be given between 6 to 9 times per day, which may limit compliance. An orally available medicinal product, such as selexipag, which, by targeting the prostacyclin pathway could affect the progressive course of PAH, would represent an important advancement in the clinical management of PAH patients, and provide a significant contribution in the treatment options for these patients.

To date, several medicinal products have been approved for the treatment of pulmonary hypertension (PH), specifically PAH. The majority of controlled trials performed in PAH have been relatively short-term studies in selected populations.

The main objective of the AC-065A303/GRIPHON OL study will be to assess the long-term safety and tolerability of selexipag in patients with PAH.

1.4.2 Patient population

The patient population will consist of:

- Patients who have completed the double-blind study AC-065A302/GRIPHON as scheduled per protocol (i.e., treated until unblinding of the study).
- Patients experiencing a morbidity event (confirmed by the Critical Event Committee [CEC]) during the study AC-065A302/GRIPHON.
- Patients who have experienced a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON and for whom a written approval to enter this study has been obtained from the sponsor.

1.4.3 Study design

The study is designed as an open-label, non-comparative, multicenter study following the AC-065A302/GRIPHON study to assess long-term safety and tolerability of selexipag in patients with PAH.

1.4.4 Comparative drug(s) and/or placebo

Not applicable

1.4.5 Dose selection

Up-titration to the individual patient's highest tolerated dose appears to be the most adequate treatment regimen for IP receptor agonists, including epoprostenol (i.v.), treprostinil (i.v., s.c. and inhaled) and iloprost (inhaled). Starting with high doses of these compounds is associated with poor tolerability due to typical prostanoid-associated

pharmacological effects such as headache, myalgia, flushing, nausea, and vomiting. Clinical experience with IP receptor agonists has shown that it is important to start at lower doses and up-titrate in order to improve tolerability.

This approach is used in the AC-065A302/GRIPHON study and will be kept in the open-label study.

During AC-065A303/GRIPHON OL, the selexipag starting dose will depend on the dose of selexipag received during AC-065A302/GRIPHON as well as at which time point of AC-065A302/GRIPHON patients are enrolled in AC-065A303/GRIPHON OL:

- Patients who enter AC-065A303/GRIPHON OL following a morbidity event during AC-065A302/GRIPHON (confirmed by the CEC) and patients experiencing a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON for whom a written approval to roll over into this study has been obtained from the sponsor will be transferred without knowledge of their previous study treatment allocation (selexipag or placebo) to preserve the integrity of the double-blind study. Therefore all these patients will enter the titration period, i.e. start treatment with selexipag at the lowest dose (200 µg b.i.d.) and will be up-titrated until their individual highest tolerated dose is reached. During the maintenance period they will receive selexipag at their individual highest tolerated dose.

- Patients who enter AC-065A303/GRIPHON OL after AC-065A302/GRIPHON Study Closure and completion of the Treatment Extension period will enter the study with knowledge of their previous study treatment allocation (selexipag or placebo) following unblinding of AC-065A302/GRIPHON:

  – Patients who were receiving selexipag will remain on the same dose they were receiving at the end of the AC-065A302/GRIPHON Treatment Extension period. If the treatment with selexipag was interrupted for 3 days or more between the last intake in study AC-065A302/GRIPHON and the initiation of selexipag in AC-065A303/GRIPHON OL, the patient will have to enter the titration period (i.e. start treatment with selexipag at the lowest dose 200 µg b.i.d.);

  – Patients who were receiving placebo will enter the titration period and start selexipag at the lowest dose (200 µg b.i.d.), and will be up-titrated until their individual highest tolerated dose is reached. They will receive selexipag at their individual highest tolerated dose during the maintenance period.

The dose of patients who did not reach the maximum of 1600 µg b.i.d. can be up-titrated based on the investigators' medical judgment, only after a site visit (scheduled or unscheduled) and in increments of 200 µg b.i.d. each time. The dose can be reduced at any time if the investigator identifies a tolerability concern for a patient.

The dose of the study drug must be up-titrated again in any case if the patients' treatment is interrupted 3 days or more between the last visit in study AC-065A302/GRIPHON and the start of study AC-065A303/GRIPHON OL, or within study AC-065A303/GRIPHON OL [Section 3.4.1].

1.4.6 Treatment duration

Study treatment for each patient lasts from his/her Visit 1 date until the end of the trial i.e., until whichever of the following occurs first: (i) selexipag is commercially available in this indication in the patient's country, (ii) the sponsor decides to stop study AC-065A303/GRIPHON OL, or (iii) the patient, or the investigator decide to discontinue study drug.

1.4.7 Primary endpoint

No primary efficacy endpoint is considered for this OL study.

1.4.8 Statistical hypotheses and sample size

No statistical hypothesis is considered for this OL study.

2 STUDY OBJECTIVES

To assess long-term safety and tolerability of selexipag in patients with PAH.

3 INVESTIGATIONAL PLAN

3.1 Overall study design

This will be a multicenter, open-label study to assess long-term safety and tolerability of selexipag in patients with PAH.

Patients (males or females aged 18 years or older) from the study AC-065A302/GRIPHON will be enrolled in this OL study [Section 1.4.2]. The study will be conducted in approximately 190 centers in 44 countries.

Visit 1 in the AC-065A303/GRIPHON OL study should correspond to the last visit in study AC-065A302/GRIPHON. If this is not possible, Visit 1 must be performed not later than 2 weeks (14 days) after the last visit in study AC-065A302/GRIPHON.

Patients who complete the AC-065A302/GRIPHON Treatment Extension period will enter the AC-065A303/GRIPHON OL study with knowledge of their previous study treatment allocation (selexipag or placebo) following unblinding of AC-065A302/GRIPHON. Patients who were receiving selexipag will enter directly into the maintenance period with the same dose they were receiving at the end of the AC-065A302/GRIPHON Treatment Extension period. Patients who were receiving placebo will enter the titration period, i.e. start selexipag at the lowest dose (200 µg b.i.d.).

Patients with a morbidity event (confirmed by the CEC), and patients experiencing worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON, and for whom a written approval to roll over into this study has been obtained from the sponsor, will be transferred from the double-blind study AC-065A302/GRIPHON to the OL study without knowledge of their previous treatment arm (selexipag or placebo) to preserve the integrity of the double-blind study. Therefore, all these patients will enter the titration period, i.e. start selexipag at the lowest dose (200 µg b.i.d.).

Each patient will have his/her selexipag dose up-titrated up to his/her individual highest tolerated dose. Patients will receive new medication bottles at Visit 1, Visit 5 and every 6 months until the end of the AC-065A303/GRIPHON OL study. If a patient enters the titration period, additional medication bottles will be given at Visit 2, 3, and 4.

At the end of the open-label study or after permanent discontinuation of study drug, the end of study (EOS) visit will be performed and a post-treatment safety follow-up period (30 days) will follow.

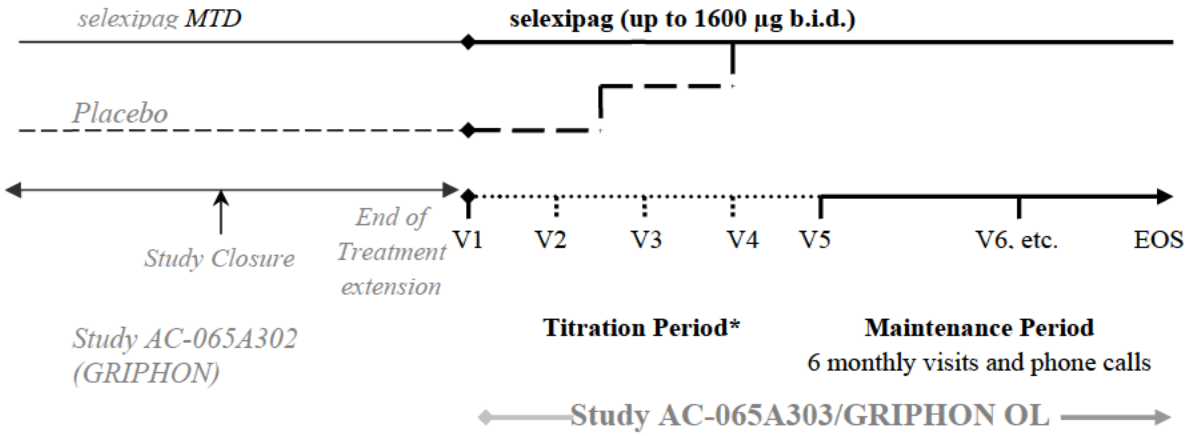
The Steering Committee involved in the study AC-065A302/GRIPHON will provide guidance on the conduct of the study.

The Ophthalmology safety board involved in the AC-065A302/GRIPHON study will be consulted for their opinion and recommendation in case of specific ophthalmological findings up to 1 July 2016 (date of disbandment of the board).

The Data Monitoring Committee involved in the study AC-065A302/GRIPHON will also review safety data from this study up to 1 July 2016 (date of disbandment of the committee).

No interim analysis is planned.

Figure 1 Study design



* Titration period only for patients with a morbidity event (confirmed by the CEC), and patients on placebo in study AC-065A302, or patient with treatment interruption ≥ 3 days

b.i.d. = twice daily; CEC = Critical Event Committee; EOS = end of study; MTD = maintenance dose; V = visit.

3.2 Study population

3.2.1 Patient population

The patient population will consist of patients who completed the double-blind treatment period of the study AC-065A302/GRIPHON and of patients who experienced a morbidity event (confirmed by the CEC) during AC-065A302/GRIPHON. Patients experiencing a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON may be enrolled after formal request from site and after written approval from the sponsor.

3.2.2 Inclusion criteria

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Patients who have completed the double-blind study, AC-065A302/GRIPHON as scheduled per protocol (i.e., treated until unblinding of the study),
   or

   Patients who have experienced a morbidity event (confirmed by the CEC) during study AC-065A302/GRIPHON,
   or

Patients experiencing a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON and for whom a written approval to roll over into this study has been obtained from the sponsor.

3. Women of child-bearing potential[3] included in study AC-065A303 must use a reliable method of contraception (with a failure rate of less than 1% per year) until 1 month after study drug discontinuation.

3.2.3 Exclusion criteria

1. Pediatric patients (i.e., < 18 years of age).
2. Patients who are not able to perform Visit 1 of AC-065A303/GRIPHON OL within 2 weeks (i.e., 14 days) of the last visit in AC-065A302/GRIPHON.
3. Patients who have started receiving prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) since the last study drug intake in AC-065A302/GRIPHON[4].
4. Severe hepatic impairment (Child-Pugh C)
5. Females who are pregnant or who plan to become pregnant during the study or are breast-feeding.
6. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence, or psychiatric disease.
7. Known hypersensitivity to selexipag or any of the excipients.

3.2.4 Concomitant medications

3.2.4.1 Allowed concomitant medications

PAH-specific therapies including ERAs, PDE-5 inhibitors, and/or riociguat.

Concomitant use of inhaled, i.v., and s.c. prostacyclin and prostacyclin analogs (e.g., epoprostenol, treprostinil, iloprost) is permitted, as deemed medically indicated by the

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[3] A woman is considered to have childbearing potential unless she meets at least one of the following criteria:
- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years with amenorrhea for at least 24 consecutive months prior to screening

[4] Single administration of i.v./inhaled prostacyclin or analogs used for acute vasodilator testing during a RHC procedure is allowed.

investigator, to stabilize a patient with worsening of PAH or to switch a patient to i.v. or s.c. treatment.

If a patient is scheduled for an intervention that may temporarily prevent him/her from taking oral medications, it is allowed to interrupt selexipag treatment and temporarily switch to another IP receptor agonist medication with a more convenient route of administration with regard to the patient's medical condition. The patient will be allowed to restart selexipag once he/she can take oral medications again. When re-starting selexipag, it is recommended to begin with the lowest dose (i.e., 1 tablet/200µg b.i.d.) and to progressively increase the selexipag dose to reach the maximum dose that was previously tolerated by the patient. The decrease of the other IP receptor agonist dose will be done in parallel with the increase of selexipag dose based on patient's individual tolerability. If the patient experiences pharmacological side effects that cannot be tolerated while he/she is concomitantly taking selexipag and the other IP receptor agonist medication, a dose reduction or stop of this other IP receptor agonist will be considered before considering a dose reduction or a stop of selexipag.

Single administration of i.v./inhaled prostacyclin or analogs used for acute vasodilator testing during a right heart catheterization (RHC) procedure is allowed.

Treatment with moderate inhibitors of CYP2C8 is allowed. If a moderate inhibitor of CYP2C8 (e.g., clopidogrel, deferasirox, teriflunomide) is concomitantly administered with selexipag, the dosing frequency of selexipag should be reduced to once daily (resulting in halving of the daily dose) unless, based on medical judgment, continuation of b.i.d. therapy is indicated. Dosing frequency of selexipag should be reverted to b.i.d. when co-administration of moderate CYP2C8 inhibitor is stopped.

Due to potential drug-drug interactions [see Section 1.3.2.1], in case of concomitant administration of rifampicin, dose adjustment of selexipag may be required.

3.2.4.2 Prohibited concomitant medications

- Due to the similar mode of action and the same route of administration, other oral IP-receptor agonists (e.g., treprostinil, beraprost) are prohibited from the last study drug intake in AC-065A302/GRIPHON until EOS in AC-065A303/GRIPHON OL.
- Concomitant administration of strong inhibitors of CYP2C8 such as gemfibrozil until EOS in AC-065A303/GRIPHON OL.
- Any investigational drug other than selexipag.

3.3 Study drug

3.3.1 Investigational drug

Patients who meet all inclusion criteria and none of the exclusion criteria will receive selexipag (200 µg tablets) at each individual patient's highest tolerated dose in addition to their usual treatment.

- The study drug will be provided by the sponsor in child-proof bottles containing 120 tablets which must not be stored above 25 °C and be protected from moisture.
- The study drug is administered orally (p.o.) in tablets of 200 µg selexipag.
- The dose regimen is b.i.d. (twice daily) with an interval of approximately 12 h.
- It is recommended to take the study medication with food.
- Depending on the highest tolerated dose of the patient, a single dose of study drug will consist of 1 to 8 tablets (200 µg to 1600 µg) b.i.d.
- If a patient was on placebo or experienced a morbidity event during AC-065A302/GRIPHON (confirmed by the CEC), he/she will enter the titration period.
- Patients already taking selexipag will continue with the same dose or will be up-titrated based on the investigators' medical judgment, only after a site visit (scheduled or unscheduled) and in increments of 200 µg b.i.d, each time. The dose cannot exceed 1600 µg b.i.d.
- Patients enrolled with a written approval from the sponsor after experiencing a worsening of PAH during the Treatment Extension period of AC-065A302/GRIPHON will enter the titration period.
- Any interruption of study drug intake of 3 days or more will require a new up-titration [Section 3.4.1]. For re-uptitration to a previously reached dose, site visits are not systematically required. In such case, re-uptitration can be done via phone calls, based on tolerability reported during the initial titration.

3.3.2 Study drug up-titration

The study drug must be up-titrated to each individual patient's highest tolerated dose in the range of 200 µg to 1600 µg b.i.d.

Patients whose dose needs to be up-titrated will start with one tablet of selexipag (200 µg) b.i.d. from Day 1. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg increments at weekly intervals during scheduled telephone calls or visits until reaching the patient's highest tolerated dose.

The decision to stop further up-titration of the dose will be based on the investigators' medical judgment, based on the occurrence and severity of typical pharmacological effects of IP receptor agonists, such as headache, jaw pain, myalgia, flushing and nausea, which cannot be tolerated by the patient. The dose will then be reduced by 200 µg b.i.d, if needed.

3.3.3 Study drug dosing scheme (titration period only)

Period	Duration	Dose regimen	
First dose	Day 1 in the evening (p.m.)	200 µg	1 tablet
Up-titration	Day 2 a.m. to Day 8 a.m.	200 µg b.i.d.	1 tablet b.i.d.
	Day 8 p.m. to Day 15 a.m.	400 µg b.i.d.	2 tablets b.i.d.
	Day 15 p.m. to Day 22 a.m.	600 µg b.i.d.	3 tablets b.i.d.
	Day 22 p.m. to Week 4 p.m.	800 µg b.i.d.	4 tablets b.i.d.
	Week 4 p.m. to Week 5 a.m.	1000 µg b.i.d.	5 tablets b.i.d.
	Week 5 p.m. to Week 6 a.m.	1200 µg b.i.d.	6 tablets b.i.d.
	Week 6 p.m. to Week 7 a.m.	1400 µg b.i.d.	7 tablets b.i.d.
	Week 7 p.m. to Week 8 a.m.	1600 µg b.i.d.	8 tablets b.i.d.

At the beginning of each up-titration phase, patients 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. It is recommended to take the study drug with food.

3.4 Study drug discontinuation and study withdrawal

3.4.1 Study drug interruption or permanent discontinuation

The investigator must interrupt or permanently discontinue the study drug if continued administration is believed to be contrary to the best interest of the patient.

In case liver impairment is suspected, a clinical assessment of severity (e.g., Child-Pugh score) should be performed. If the investigator becomes aware that a patient has developed moderate hepatic impairment (e.g., Child-Pugh B) at any time during the AC-065A302/GRIPHON or the AC-065A303/GRIPHON OL study, then it is the responsibility of the investigator to evaluate the benefit-risk of keeping the patient on study drug. In case a patient has developed severe hepatic impairment (e.g., Child-Pugh C), the study drug must be discontinued. Assessment of Child-Pugh score is not a mandatory study assessment.

Should signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. If confirmed, selexipag must be discontinued.

The interruption or permanent discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., ECG or laboratory abnormalities), or for administrative reasons, in particular withdrawal of the patient's consent. The reason for study drug interruption or permanent discontinuation must be documented in the CRF.

Any study drug interruption of 3 days or more will require new up-titration. Patients will start again with 1 tablet of selexipag (200 µg) b.i.d. If this dose is well tolerated, the dose will be up-titrated by the investigator in 200 µg increments up to the patient's highest tolerated dose before study drug interruption. For each patient, the up-titration frequency will be up to the medical judgment of the investigator and based on his/her clinical evaluation of the patient's tolerability to study drug prior to its interruption.

Interruptions of 1 day and more must be recorded on the study drug log in the CRF.

3.4.2 Patient's follow-up after study drug discontinuation

An EOS visit must be performed [Section 3.10.4] after permanent discontinuation of the study drug. It is recommended to perform the EOS visit within 7 days of the last study drug intake. The patient will be followed for 30 days after the permanent study drug discontinuation to collect information on SAEs. If discontinuation is considered study drug-related, the patient will remain under the supervision of the investigator until satisfactory health has returned.

3.4.3 Study withdrawal

A patient will be considered as withdrawn from the study if, and only if, he/she withdrew consent or is lost to follow-up after exhausting all means of contact.

The potential follow-up of patients after their withdrawal of consent will depend upon local regulations or specific agreement with the patients.

3.4.4 Study completion

The overall study is considered completed when all patients have completed their individual safety follow-up phone call or have died, withdrawn consent or have been lost to follow-up.

3.4.5 Replacement policy

3.4.5.1 Patients

Patients prematurely discontinued from the study drug for any reason will not be replaced.

3.4.5.2 Centers

Not applicable.

3.5 Treatment exposure, compliance and drug accountability

Records of study drug used, dosages administered, and intervals between visits, are kept during the study. Study drug accountability is performed on an ongoing basis by the study staff and checked by the monitor during site visits and at completion of the study. Patients are asked to return all unused study drug at each visit.

3.6 Treatment assignment

3.6.1 Treatment assignment

Not applicable

3.6.2 Blinding

Not applicable.

3.6.3 Emergency procedure for unblinding

Not applicable.

3.7 Study drug packaging and labeling

3.7.1 Study drug packaging

Actelion will provide study drug as tablets in child-proof bottles containing 120 tablets.

3.7.2 Study drug labeling

The labeling and packaging of selexipag will be conducted according to Good Manufacturing Practice, Good Clinical Practice, and any local or national regulatory requirements.

3.7.3 Study drug storage and dispensing

The investigator is responsible for the safe and proper handling and storage of the study drug at the investigational site, and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol.

Study drug must be kept in a locked room, which can only be accessed by the pharmacist, the investigator, or another duly designated person. The study drug must not be stored above 25°C and must be protected from moisture. The study centers will be supplied with study drug according to the centers' needs, depending on the number of patients participating in the study. The site should check at regular intervals whether enough medication is available.

Patients will receive medication bottles at Visit 1, (Visit 2, Visit 3, and Visit 4, for the titration period, if applicable), Visit 5, and at the 6-monthly visits thereafter, up to EOS. The patient will receive enough study medication at each of these visits.

Each medication bottle will have a label with a tear-off part specifying the study protocol number and the batch number. When the medication is issued to the patient, the investigator or pharmacist must remove the tear-off part and affix it to the Drug Dispensing Log.

3.8 Study endpoints

3.8.1 Efficacy endpoints

Not applicable.

3.8.2 Safety and tolerability endpoints

- Treatment-emergent AEs up to 3 days after study drug discontinuation.
- Treatment-emergent SAEs up to 3 days after study drug discontinuation.
- AEs leading to permanent discontinuation of study drug.

3.9 Study assessments

3.9.1 Safety and tolerability assessments

The definitions, reporting and follow-up of AEs, SAEs and potential pregnancies are described in Section 4.

3.9.1.1 Vital signs and body weight

Vital signs (blood pressure and heart rate) and body weight will be assessed at each visit and recorded in the CRF.

3.9.1.2 Laboratory assessments

3.9.1.2.1 Type of laboratory

Both central and local laboratories are used in the study.

Until approval of global protocol Version 4, blood sample analysis (hematology and biochemistry) is to be performed by local laboratories. For all the blood samples analyzed up to approval of the global protocol Version 4, anonymized copies of the print-outs of the local laboratory reports will be sent to the central laboratory in original language together with the local normal ranges valid at the time of analysis. In case re-test or unscheduled blood samples were analyzed between regular visits for the purpose of monitoring an adverse event, the lab reports will also be collected. The central laboratory will be responsible for entering the results into a database, converting the results and normal ranges to SI units, and transferring all data to Actelion.

After approval of the global protocol Version 4, the hematology and biochemistry blood samples must be sent to the central laboratory for analysis (see contact details on page 2). The central laboratory reports will be available to the investigator. In case a complete or

partial re-test is deemed necessary to follow up an AE or to verify an unexpected abnormal value, the re-test blood sample should also be analyzed by the central laboratory.

The results (whether obtained via local or central laboratory) will be kept in the patient's file. Any clinically significant laboratory abnormality must be reported by the investigator as an AE and/or SAE, as appropriate [Section 4].

Details about collection and shipment of samples, and the reporting of results and abnormalities, can be found in the laboratory manual provided to the investigator.

3.9.1.2.2 Laboratory parameters

Hematology and blood chemistry

Hematology and blood chemistry tests will be performed at Visit 1, if the last assessments in AC-065A302/GRIPHON were performed more than 4 weeks ago, and then at every visit until EOS. They include hemoglobin, hematocrit, platelet, leukocyte and erythrocyte counts, liver aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, creatinine, urea, glucose, sodium, potassium, and albumin.

Local assessment of thyroid function (Thyroid-stimulating hormone, free triiodothyronine, free thyroxin) may be performed for individual patients if deemed clinically indicated by the investigator.

Pregnancy test (for women of childbearing potential)

Monthly urine (or serum) pregnancy tests must be performed from Visit 1 and up to at least 1 month after permanent discontinuation of the selexipag treatment. The monthly urine pregnancy tests are performed by the patient at home with validated kits provided by the site, or during a scheduled visit, or in a local laboratory. A serum pregnancy test is mandatory if pregnancy is suspected during the course of the study. Results of pregnancy tests will be documented in the patient's records (pregnancy test card).

Any pregnancy occurring during the treatment period and up to 30 days after study drug discontinuation must be reported immediately to the Actelion Drug Safety Department using the Actelion Pregnancy Form [Section 4].

3.9.2 Physical examination and concomitant medications

3.9.2.1 Physical examination

Physical examination (i.e., inspection, percussion, palpation and auscultation) is performed at every visit up to EOS. Clinically relevant findings meeting the definition of an AE (new AE or worsening of previously existing condition) must be documented in patient's medical records and noted on an AE page of the CRF.

3.9.2.2 Concomitant medications

All concomitant medications (ongoing, initiated, discontinued) including PAH specific medications and diuretics taken in the period between Visit 1 and up to EOS will be recorded on the Concomitant Medication pages of the CRF. Any dose changes in PAH specific medications (e.g., ERAs, PDE-5 inhibitors, riociguat, prostacyclin, prostacyclin analogs, and initiation of continuous chronic oxygen therapy) must be recorded in the CRF.

3.10 Visit and assessment schedule

For a tabulated summary of all visits and assessments described in the following sections see Table 1.

3.10.1 Visit 1

Visit 1 should correspond to the last visit in AC-065A302/GRIPHON or, if not possible, must be within 2 weeks (14 days) of the last visit in study AC-065A302/GRIPHON.

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this OL study after adequate explanation of the aims, methods and objectives of the study.

The informed consent form (ICF) must be signed and dated at the latest during the Visit 1 and prior to the execution of any study assessment or procedure.

The visit includes:

- Physical examination
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Hematology
  - Blood chemistry
- Urine pregnancy test (for women of childbearing potential)
- Concomitant medication
- Dispensing of study drug.

If Visit 1 is performed on the same day as the last visit (EOS visit or End of Treatment Extension visit) in AC-065A302/GRIPHON, assessments that are common to both studies are not to be repeated. Results are to be reported in the CRF pages of both studies.

The laboratory tests are not to be repeated if they were performed within 4 weeks of this visit.

3.10.2 Titration period (if applicable)

3.10.2.1 Week 1 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (2 tablets selexipag b.i.d.)

3.10.2.2 Week 2 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (3 tablets selexipag b.i.d.)

3.10.2.3 Week 3 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (4 tablets selexipag b.i.d.)

3.10.2.4 Visit 2 (Week 4)

- Physical examination
- Recording of AEs/SAEs
- Concomitant medication
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Hematology
  - Blood chemistry
- Urine pregnancy test (for women of childbearing potential)
- Dispensing of study drug (selexipag).
  - Titration to next dose (5 tablets selexipag b.i.d.)

3.10.2.5 Week 5 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (6 tablets selexipag b.i.d.)

3.10.2.6 Week 6 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (7 tablets selexipag b.i.d.)

3.10.2.7 Week 7 (telephone call)

- Recording of AEs/SAEs
- Titration to next dose (8 tablets selexipag b.i.d.)

3.10.2.8 Visit 3 (Week 8)

- Physical examination
- Recording of AEs/SAEs
- Concomitant medication
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Hematology
  - Blood chemistry
- Urine pregnancy test (for women of childbearing potential)
- Dispensing of study drug (selexipag).

3.10.2.9 Week 12 (telephone call)

- Recording of AEs/SAEs
- Urine pregnancy test result for women of childbearing potential

3.10.2.10 Visit 4 (Week 16)

- Physical examination
- Recording of AEs/SAEs
- Concomitant medication
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Hematology
  - Blood chemistry
- Urine pregnancy test (for women of childbearing potential)
- Dispensing of study drug (selexipag)

3.10.3 Maintenance period

3.10.3.1 Visit 5 and 6-monthly visits (Visit 6, 7, etc.)

From Visit 5 onwards, all following visits are scheduled every 6 months ± 7 days. In between the 6-monthly visits, the investigator will call the patient to assess safety and tolerability by inquiring about AEs and SAEs.

The morning dose of the study drug should be taken as usual.

These visits include:

- Physical examination
- Recording of AEs/SAEs
- Concomitant medication
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Hematology
  - Blood chemistry
- Urine pregnancy test (for women of childbearing potential)
- Dispensing of study drug (selexipag) for a 6 months' treatment period.

3.10.3.2 Telephone call Month 9 (and every 6 months thereafter)

Telephone calls are performed every 6 months, alternating with the 6-monthly visits. For patients who do not perform the titration period, the first phone call will occur at Week 12.

- Recording of AEs/SAEs
- Urine pregnancy test result for women of childbearing potential

3.10.4 End of study visit or permanent discontinuation of study drug

Actelion will notify all sites when the end of study will occur. It can be at different dates depending on the sites and/or the country (see definition in Section 1.4.6). For all patients still participating to the study, the EOS visit must be scheduled within 4 weeks after the end of study notification.

For patients prematurely discontinuing selexipag treatment, it is recommended to perform the EOS visit within 7 days of the last study drug intake.

This visit includes:

- Physical examination
- Recording of AEs/SAEs
- Concomitant medication
- Measurement of vital signs and body weight
- Laboratory tests including:
  - Hematology
  - Blood chemistry
- Urine pregnancy test (for women of childbearing potential)
- Return of unused medication including empty bottles.

3.10.5 30-day follow-up

All patients will be contacted by phone 30 to 37 days after study drug discontinuation (safety follow-up call) [Sections 4.2.4 and 4.3.2].

- Urine pregnancy test result for women of childbearing potential

3.10.6 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., loss of efficacy, AE, study drug dispensing, etc.), appropriate assessments may be performed based on the medical judgment of the investigator. Assessments that are included in the protocol schedule of assessments will be recorded in the CRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Summary table

Periods	Treatment	Follow-up	After follow-up
Timeframe	During study drug administration and until 3 days after last study drug administration	From 3 days to 30 days after study drug discontinuation	After 30 days
AE/SAE reporting on CRF AE page	All AEs/SAEs (treatment-emergent[1])	None	None
SAE reporting on SAE form	All SAEs (treatment-emergent[1])	All SAEs	If felt appropriate by investigator
Final study report	Analyzed	Described	Might be described

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

The resolution date and outcome of AEs reported during the double-blind study AC-065A302/GRIPHON that are ongoing at the time of the patient's Visit 1 in AC-065A303/GRIPHON OL, must be recorded on specific CRF pages (Ongoing AEs from the GRIPHON study). If the AE worsens (i.e., changes intensity, seriousness or relationship) during AC-065A303/GRIPHON OL, a new AE must be recorded on the standard AE pages with the onset date equal to the date of worsening.

4.2 Adverse events

4.2.1 Definitions of adverse events

An AE is any adverse change from the subject's/patient's baseline condition, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation up to 3 days after study drug discontinuation), whether or not considered related to the study drug.

Adverse events 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 after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose of study drug must be mentioned in the Study Drug Log. For selexipag, "overdose" is defined as the intake of any single dose greater than 1600 μg (8 tablets) or a total daily dose greater than 3200 μg (16 tablets).

4.2.2 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 CRF.

If the intensity of an AE worsens during study drug 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.

The three categories of intensity are defined as follows:

- *Mild*

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

- *Moderate*

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

- *Severe*

The event may cause noticeable discomfort, and usually interferes with daily activities. The subject/patient 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 [Section 4.3.1]. These terms are used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction). However, a severe event (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day [Section 4.3.1.2]. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments (e.g., ECG findings) considered as AEs. The investigator should tick "non-applicable" on the AE page of the CRF to qualify the intensity of the AE.

4.2.3 Relationship to study drug

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study drug, and reported as either related or unrelated.

Related to study drug

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted or discontinued.
- The event reoccurred when treatment was reintroduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

Unrelated to study drug

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

4.2.4 Reporting of adverse events

All AEs occurring after study drug initiation and up to 3 days after study drug discontinuation must be recorded on specific AE pages of the CRF.

All AEs ongoing from the AC-065A302/GRIPHON study must be reported on the dedicated AC-065A303/GRIPHON OL CRF pages and outcome must be reported when it is known.

4.2.5 Follow-up of adverse events

Adverse events still ongoing after study drug discontinuation for a given patient must be followed until 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained.

4.3 Serious adverse events

4.3.1 Definitions

4.3.1.1 Serious adverse events

An SAE is defined by the International Council for Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring inpatient hospitalization, or prolongation of existing hospitalization
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically significant, or requires intervention to prevent at least one of the outcomes listed above.

Life-threatening refers to an event in which the subject/patient 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.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject/patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

4.3.1.2 Hospitalization – prolongation of existing hospitalization

The following reasons for hospitalizations are not considered AEs, and are therefore also not SAEs:

- Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

4.3.1.3 Serious adverse events related to study-mandated procedures

A SAE is defined as related to study-mandated procedures if it appears to have a reasonable possibility of a causal relationship (i.e., a relationship cannot be ruled out) to such procedures (other than administration of study drug). Examples of study-mandated procedures include complication of a mandated invasive procedure such as blood sampling, or a car accident on the way to the hospital for a study visit, etc.

4.3.2 Reporting of serious adverse events

4.3.2.1 Screening period

Serious adverse events occurring between signing the ICF and study drug initiation are only required to be reported if they are considered by the investigator to be related to study-mandated procedures.

As these SAEs are not reported as AEs in the CRF, they are collected only on an SAE form, and entered only into the drug safety database.

4.3.2.2 Treatment period

All SAEs, regardless of causal relationship, must be reported, including those related to study-mandated procedures. Those SAEs occurring during study drug administration, i.e., between study drug initiation and three days after study drug discontinuation, are defined as treatment-emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the CRF. They are therefore entered into both the drug safety and clinical databases, and must be reconciled before study closure.

4.3.2.3 Follow-up period

All SAEs regardless of causal relationship occurring from 3 days after study drug discontinuation until 30 days after study drug discontinuation must be reported.

All SAEs occurring during the follow-up period must be recorded on an SAE form. These SAEs are therefore entered only into the drug safety database.

4.3.2.4 Reporting procedures

All new SAEs as well as new information regarding SAEs ongoing from the AC-065A302/GRIPHON study must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the patient, and whether or not this event is considered by the investigator to be related to study drug. These SAE forms must be faxed to the Actelion drug safety department (contact details for which are provided at the beginning of this protocol). The investigator must complete the SAE form in English (unless otherwise specified), and must assess the relationship of the event to study drug.

Such preliminary reports will be followed by detailed descriptions that may include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

Suspected (considered related to the study drug) Unexpected (not previously described in the reference safety document) Serious Adverse Reactions (SUSARs) will be expedited by Actelion to Health Authorities, ECs/IRBs and investigators, as appropriate.

The reference safety document to assess expectedness of a suspected serious adverse reaction and need for reporting by the sponsor to regulatory authorities, ECs/IRBs, and investigators is the Investigator's Brochure [Selexipag IB, section 6 Reference Safety Information].

The following events are anticipated to occur in subjects with PAH, and will be considered as 'disease-related': signs and symptoms of PAH worsening/exacerbation/ progression, abdominal pain, anorexia, chest pain, cyanosis, diaphoresis, dizziness, pre-syncope, syncope, dyspnea, orthopnea, fatigue, hemoptysis, heart failure, hypoxia, palpitations, collapse, systemic arterial hypotension, and tachycardia. These events therefore do not require expedited reporting to Health Authorities, ECs/IRBs, and investigators. Like all other SAEs, these SAEs must be reported on an SAE form by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event, and be reported on the AE page of the CRF.

4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event is otherwise explained.

4.3.4 Reporting of serious adverse events after the 30-day follow-up period

New SAEs occurring at any time after the 30-day follow-up period after study drug discontinuation may be reported on a SAE form to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event, if considered related to the previous exposure to study drug by the investigator. These SAEs are only entered in the drug safety database, and hence will not affect study closure.

4.4 Pregnancy

4.4.1 Teratogenicity

In the reproductive and developmental toxicity studies in animals, no changes were observed in fertility and teratogenicity.

However, appropriate precautions must be taken by women of childbearing potential. Women must not become pregnant during the study and up to 1 month after study drug discontinuation.

If a woman becomes pregnant while on study drug, permanent discontinuation of study drug must be considered. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

4.4.2 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring during study drug administration or during the first month following study drug discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion drug safety department (see contact details provided on the pregnancy form), and on an AE page of the CRF, as applicable.

4.4.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Actelion drug safety department.

Such follow-up information will only be entered in the drug safety database, and hence will not affect study closure.

5 STATISTICAL METHODOLOGY AND ANALYSES

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

This is an open-label extension study. No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

5.1 Populations for analyses

For purposes of analysis, the following populations are defined:

All patients who sign an ICF / ICFs will be used for disposition summary.

All analyses will be performed on the selexipag-initiated set (SIS) that comprises all patients who initiated selexipag treatment at any time during AC-065A302/GRIPHON or AC-065A303/GRIPHON OL study. The baseline for this analysis set is the last assessment before selexipag initiation.

5.2 Statistical analyses

5.2.1 Efficacy analyses

Not applicable.

5.2.2 Safety analyses

5.2.2.1 Adverse events

The verbatim terms entered in the CRF by investigators to denote adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the selexipag treatment phase (up to 3 days after the treatment end) or AEs that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of patients who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, or figures may be provided, as appropriate, for those patients who die, who discontinue selexipag treatment due to an AE, or who experience a severe or a serious AE.

AEs of special interest, based on the latest risk management plan at the time of database lock, will be summarized.

5.2.2.2 Clinical laboratory tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at selected scheduled time points. Frequency tabulations of the treatment-emergent marked laboratory abnormalities will be presented. A listing of patients with any laboratory results outside the reference ranges will be provided. A listing of patients with any markedly abnormal laboratory results will also be provided.

5.2.2.3 Vital signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at selected scheduled time points. The percentage of patients with values beyond clinically important limits will be summarized.

6 PROCEDURES AND GOOD CLINICAL PRACTICE

6.1 Procedures

6.1.1 Protocol amendments

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or Health Authorities. An amendment could therefore occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by Actelion, and must be reviewed by the Coordinating/Principal Investigator or Steering Committee, as appropriate.

Changes to the Core Subject/Patient Information and Informed Consent requested by ECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

6.1.1.1 Non-substantial amendment

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., Actelion instead of CRO monitors), or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and Health Authorities (subject to national regulations).

6.1.1.2 Substantial amendment

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of subjects/patients, and changes to the objectives or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Subject/Patient Information and Informed Consent.

Substantial amendments must be approved by the appropriate ECs/IRBs, and in some jurisdictions by the Health Authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities, and must be signed by the investigators.

6.1.1.3 Urgent amendment

An urgent amendment might become necessary to preserve the safety of the subjects/patients included in the study. The requirements for approval must not prevent any immediate action being taken by the investigators or Actelion in the best interests of the subjects/patients. If deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases the implementation of urgent amendments will occur before submission to, and approval by, ECs/IRBs and Health Authorities.

In such cases, the investigator must notify Actelion within 24 hours. A related substantial amendment will be prepared and submitted by Actelion to the appropriate ECs/IRBs and Health Authorities within 10 working days of receiving the notification.

6.1.2 Monitoring

The monitor will contact and visit the investigator regularly, and on request must be permitted to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents, provided that patient confidentiality is maintained in accordance with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. Actelion monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan.

The rules regarding identification of any data recorded directly on the CRFs and considered to be source data are specified in the following document: Site Guidelines and CRF Completion Guideline. The investigator must ensure that subject/patient anonymity is maintained. On CRFs or other documents submitted to Actelion, subjects/patients must

be identified only by number, and never by name. The investigator must keep a subject/patient identification log showing the subject number, the subject/patient's name, date of birth and any other locally accepted identifiers. Documents identifying the subjects/patients (e.g., signed informed consent forms) should not be sent to Actelion, and must be kept in strict confidence by the investigator.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject/patient is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In the case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first patient is included in the study. Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

6.1.3 Data management

6.1.3.1 Data collection

A Subject Enrollment Log will be completed for all patients enrolled in the study.

For each patient enrolled, regardless of study drug initiation, a paper CRF must be completed and signed by the principal investigator or co-investigator. This also applies to those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis and will be collected by the monitor(s).

All case report forms must be completed in a legible way. Errors must be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the Principal Investigator, co-investigator, or study nurse. Detailed descriptions of how to complete the CRF, including the use of either a digital or a standard ballpoint pen, can be found in the current version of the CRF completion guidelines.

6.1.3.2 Database management and quality control

All data from the CRF will be entered into the database twice, by two different individuals.

The entered data will be systematically checked by Actelion staff, using error messages printed from validation programs and database listings. Errors with obvious corrections will be corrected and communicated to the site. Data clarification requests will be entered on Data Clarification Forms, which will be returned to the investigational site for resolution. A copy of the signed Data Clarification Form is to be kept with the CRFs, and once received at Actelion, the resolutions will be entered into the clinical database.

A second review of the data will be performed by medically trained staff.

Quality control audits of the database will be made before study closure.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Global Trial Leader and the Head of Clinical Development.

6.1.4 Recording of data and retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, and the study data to be subsequently verified. These documents are to be classified into two different categories: investigator's file, and patient clinical source documents.

The investigator's file will contain the protocol and all protocol amendments, the FDA form 1572 for studies conducted under a US IND, a financial disclosure form, the CRFs and data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curricula vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence in accordance with ICH GCP and local regulations.

Subject/patient clinical source documents include, but are not limited to, hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as is necessary to comply with national and international regulations (generally 2 years after either discontinuation of clinical development, or the last marketing approval, of the investigational drug). No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

When source documents are required for the continued care of the subject/patient, appropriate copies should be made for storing off site.

6.1.5 Audit

The Actelion Global Quality Management Department may conduct audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to evaluate compliance with the principles of GCP- and ICH-related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by a Health Authority, the investigator must inform Actelion immediately that such a request has been made.

The investigator must permit such audits by Actelion or Health Authorities, and must facilitate them by providing access to the relevant source documents.

6.1.6 Handling of study drug(s)

Actelion will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. 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. An accurate record of the date and amount of study drug(s) dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only in accordance with this protocol, and not for any other purpose. The responsible person must not destroy any drug labels or unused drug supply. On termination of the study, the monitor will collect used and unused study drug bottles which will be sent to the warehouse, where the sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers may be destroyed at the site once drug accountability is final and has been checked by the sponsor or its deputy, and written permission for destruction has been obtained from Actelion.

6.1.7 Publication and reporting of study results

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the Coordinating Investigator (or Principal Investigator for single-center studies).

In accordance with standard editorial and ethical practice, the results of Actelion-sponsored studies will be published. Results from multicenter studies must be published or presented at congresses only in their entirety and not as individual center data, except for ancillary studies.

The Coordinating Investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

Any study-related article or abstract written independently by investigators must be submitted to Actelion for review at least 60 days prior to submission for publication or presentation.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of Actelion, and will be determined by mutual agreement.

6.1.8 Disclosure and confidentiality

By signing this protocol, the investigator agrees to keep all information provided by Actelion in strict confidence, and to request similar confidentiality from his or her staff and the EC/IRB. Study documents provided by Actelion (including Investigator's Brochures, protocols, CRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by Actelion to the investigator may not be disclosed to others without direct written authorization from Actelion, except to the extent necessary to obtain informed consent from subjects/patients who wish to participate in the trial.

6.1.9 Premature termination or suspension of the study

Both Actelion and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, Actelion will promptly inform the investigators, the ECs/IRBs and Health Authorities, as appropriate, and provide the reasons for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with Actelion must promptly inform all enrolled subjects/patients, and ensure their appropriate treatment and follow-up.

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

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

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

6.2 Good Clinical Practice

6.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the 'Declaration of Helsinki' (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh and Seoul), and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided to each investigational site.

All studies must follow ICH GCP Guidelines and, if applicable, the US Code of Federal Regulations. In other jurisdictions in which GCP Guidelines exist, the investigators will strictly ensure adherence to the stated provisions.

6.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject/patient (such as subject/patient information used to obtain informed consent) to an EC or IRB. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the trial, the documents reviewed, and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations [Section 6.1.1].

6.2.3 Informed consent

It is the responsibility of the investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to the subjects/patients that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason. Appropriate forms for documenting informed consent will be provided to the sites prior to the study.

The Informed Consent and Patient Information will be provided in the local language.

6.2.4 Compensation to subjects and investigators

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

The compensation of the subject/patient in the event of study-related injuries will comply with applicable regulations.

7 REFERENCES

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Actelion Pharmaceuticals Ltd
Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

Protocol Title
AC-065A303: Long-term single-arm open-label study, to assess the safety and tolerability of selexipag (ACT-293987) in patients with pulmonary arterial hypertension

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GRIPHON OL

Protocol AC-065A303; Phase 3

JNJ-67896049/ACT-293987 Selexipag

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

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

EudraCT NUMBER: 2009-014992-31

Status: Approved
Date: 16 June 2020
Prepared by: Janssen Research & Development, LLC; Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document number: D-20.209

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 patients 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 patient 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 patients and site staff. If, at any time, a patient's safety is considered to be at risk, study drug 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, patients will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Patients 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 patients on study drug, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the patient, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study drug 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 patient has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study drug and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

In addition to the general measures described above, certain protocol-specific measures may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity, and in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

- **Related to Protocol Section 3.9.1.2.1:** "Analyses of blood samples for hematology and biochemistry are to be performed by a central laboratory. In case a re-test is necessary, this

should also be analyzed by the central laboratory". If a patient cannot visit the site, the investigator will judge whether the patient needs to go to a certified local laboratory close to the patient's home in order to perform specific laboratory tests or if these can be delayed. If the patient can visit the site but central laboratory kits are not available due to customs delay related to COVID-19, the site can use the hospital laboratory facilities. Missed or delayed laboratory tests and replacement of central laboratory by local laboratory will be captured in the clinical database and in the clinical trial management system, and will be identified as such under "COVID-19-related protocol deviation".

- **Related to Protocol Section 3.7.3:** "Patients will receive medication bottles at the 6-monthly visits from Visit 5 up to EOS". For patients unable to visit the clinic/hospital, direct-to-patient (DTP) shipment of study drug may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP shipments are deemed necessary, the process should be coordinated between the site and sponsor staff following the "COVID-19 DTP Guidance Document".
- **Related to Protocol Section 6.2.3:** Informed consent. Consenting and reconsenting of patients 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.

Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Temporary or permanent discontinuations of study drugs for a COVID-19 related issue (other than adverse event) should be documented with the prefix "COVID-19-related" in the case report form (CRF). Instructions for data entry are described in the CRF completion 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.

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD , MD

Institution: Actelion Pharmaceuticals Ltd

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.