Selexipag / ACT-293987

Pulmonary Arterial Hypertension

Protocol AC-065A309

A multicenter, open-label, single-sequence cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag

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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Selexipag / ACT-293987

Indication

Pulmonary arterial hypertension

Protocol number, study title

AC-065A309

A multicenter, open-label, single-sequence cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag.

I approve the design of this study.

Title	Name	Date	Signature
Clinical Trial Physician	[redacted]	[redacted]	[redacted]
Clinical Trial Statistician	[redacted]	[redacted]	[redacted]

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Selexipag / ACT-293987

Indication

Pulmonary arterial hypertension

Protocol number, study title

AC-065A309

A multicenter, open-label, single-sequence cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag.

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

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 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	Site number	Town	Date	Signature
Principal Investigator					

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LIST OF ABBREVIATIONS AND ACRONYMS

ACT-333679	The active metabolite of selexipag
AE	Adverse event
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from 0 to infinity
$AUC_{\tau, ss}$	Area under the plasma concentration-time curve during a dose interval at steady state
b.i.d.	Twice a day
BLQ	Below the limit of quantification
CI	Confidence interval
$C_{max, ss}$	Maximum plasma concentration at steady state
CRA	Clinical Research Associate
CRF	Case Report Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
$C_{trough, ss}$	Trough plasma concentration at steady state
CV	Coefficients of variation of arithmetic mean
CV_b	Inter-subject coefficient of variation
CV_{ln}	Coefficients of variation of geometric mean
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EOS	End-of-Study
ERA	Endothelin receptor antagonist
FC	Functional Class
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
i.v.	Intravenous
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP receptor	Prostacyclin receptor
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LC-UV	Liquid chromatography with UV detector
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MLA	Marked laboratory abnormality
PAH	Pulmonary arterial hypertension
PDE-5	Phosphodiesterase type-5
PI	Principal Investigator
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PT	Preferred Term
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RSI	Reference safety information
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error

sGC	Soluble guanylate cyclase
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SOC	System Organ Class
$t_{max, ss}$	Time to reach maximum plasma concentration at steady state
USPI	United States Package Insert
WHO	World Health Organization

PROTOCOL SYNOPSIS AC-065A309

TITLE	A multicenter, open-label, single-sequence cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag
OBJECTIVES	**Primary objective(s)** The primary objective of this study is to assess whether temporary switching from a stable oral dose of selexipag to an intravenous (i.v.) dose of selexipag providing comparable exposure to active metabolite ACT-333679 and switching back to the initial oral dose of selexipag is safe and well tolerated in subjects with stable pulmonary arterial hypertension (PAH). **Other objectives** Other objectives are described in Section 2.2.
DESIGN	This is a prospective, multi-center, open-label, single-sequence, cross-over, Phase 3 study. Subjects with stable PAH, currently treated with Uptravi® at a stable dose (i.e., unchanged dose for 28 days), will be enrolled. Subjects will be hospitalized during Period 1 (pre-treatment period) and Period 2 (treatment period). No interim analysis is planned.
PERIODS	**Screening period:** Up to 28 days; starts with the signing of the Informed Consent Form (ICF) and ends with first day (Visit 2, Day 1) of Period 1 (Uptravi, pre-treatment period). **Treatment and observation period:** The treatment and observation period includes the following consecutive periods: • Period 1 (Uptravi, pre-treatment period, in-hospital): 1 day Starts with intake of the morning dose of Uptravi at Visit 2 Day 1 and ends the following day, before initiation of the first infusion of i.v. selexipag.

	• Period 2 (i.v. selexipag, treatment period, in-hospital): 36 hours (3 doses) Starts in the morning of Visit 2 on Day 2 with the start of the first infusion of i.v. selexipag and ends in the evening of Visit 2 on Day 3 before the evening administration of Uptravi. Note: oral administration of Uptravi is interrupted during the treatment period with i.v. selexipag. • Period 3 (Uptravi, post-treatment period): 7 to 11 days Starts in the evening of Visit 2 on Day 3 with the oral administration of Uptravi and ends 7 to 11 days later, at Visit 3. **Safety Follow-up period:** Starts at the end of Visit 3 and ends 30 to 37 days after the last administration of i.v. selexipag with the End-of-Study telephone call (Visit 4).
PLANNED DURATION	Approximately 9–12 months from first subject first visit to last subject last visit.
SITE(S) / COUNTRY(IES)	10 sites in 2 countries (planned).
SUBJECTS / GROUPS	Approximately 20 subjects will be enrolled in order to obtain 18 evaluable subjects. Two different groups of subjects will be enrolled based on their dose of Uptravi: • Group A: Subjects with a stable dose of Uptravi between 200 and 1000 µg twice daily (b.i.d.; inclusive): at least 5 and up to 8 subjects will be enrolled in this dose group. • Group B: Subjects with a stable dose of Uptravi between 1200 and 1600 µg b.i.d. (inclusive): At least 12 and up to 15 subjects will be enrolled in this dose group.
INCLUSION CRITERIA	1. Signed ICF prior to any study-mandated procedure. 2. Male and female subjects at least 18 to 75 years inclusive. 3. Subjects with PAH belonging to the Updated Clinical Classification Group 1 [Galiè 2016] 4. Subjects who have been prescribed Uptravi in compliance

	with local prescribing information (i.e., SmPC or USPI). 5. Stable PAH defined as WHO Functional Class (FC) I–III at Visit 1 and Visit 2 and no change (i.e., introduction or dose change) in PAH-specific medication (i.e., ERA, PDE-5 inhibitor or sGC stimulator) and diuretics in the last 28 days prior to Visit 2. 6. Subjects currently treated with Uptravi at a stable dose (i.e., unchanged dose) for at least 28 days before Visit 2. 7. A woman of childbearing potential is eligible only if she has a negative urine pregnancy test at Visit 1 and at Visit 2.
EXCLUSION CRITERIA	1. Pregnant, planning to become pregnant or lactating. 2. Known and documented moderate or severe hepatic impairment. 3. Subjects having received gemfibrozil at any time since initiation of Uptravi. 4. Treatment with any prostacyclin and prostacyclin analogs within 28 days prior to Visit 1. 5. SBP < 90 mmHg at Visit 1 or at Visit 2. 6. Known or suspected uncontrolled hyperthyroidism. 7. Severe renal failure and ongoing or planned dialysis. 8. 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. 9. Known concomitant life-threatening disease with a life expectancy < 12 months. 10. Treatment with another investigational treatment within 3 months of Visit 1.
STUDY TREATMENTS	**Investigational treatment** The study treatment (i.v. selexipag) will be administered b.i.d. intravenously as an infusion over an 87 minute period [see Section 5.1.4]. The dose of i.v. selexipag will be individualized for each subject and will aim to reach an exposure to the active metabolite (area under the concentration-time curve [AUC] between two doses) comparable to the one obtained with subject's current oral dose of Uptravi. **Comparator and/or placebo** Not applicable.

AUXILIARY MEDICINAL PRODUCTS	The study population consists of subjects who have been prescribed Uptravi (oral selexipag) as part of their standard PAH treatment (i.e., Uptravi must not have been prescribed solely for the purpose of the study). Subjects will keep using Uptravi during their participation in the study as prescribed by their physician and in compliance with the USPI/SmPC [Uptravi® SmPC; Uptravi® USPI] including the use of contraception for women of childbearing potential. Subject's oral treatment with Uptravi will be temporarily interrupted for 36 hours during the administration of study treatment (i.v. selexipag).
ENDPOINTS	**Primary efficacy endpoint(s)** Not applicable. **Secondary efficacy endpoints** Not applicable. **Main safety and tolerability endpoints** The main safety and tolerability endpoints will be analyzed over the Period 1, Period 2, and Period 3 combined. • Discontinuations due to prostacyclin-associated adverse events (AEs). • AEs and serious AEs (SAEs). • Prostacyclin-associated AEs. • AEs related to injection site reactions. • PAH-related AEs. **Other endpoints** Other endpoints are described in Section 6.2.3.
PHARMACOKINETIC ENDPOINTS	• The AUC during a dose interval at steady state ($AUC_{\tau, ss}$) of selexipag and its active metabolite, ACT-333679, at steady state after Uptravi (oral selexipag) in Period 1 and after i.v. selexipag administration in Period 2. • The maximum plasma concentration at steady state ($C_{max, ss}$) of selexipag and its active metabolite, ACT-333679 after Uptravi (oral selexipag) in Period 1 and i.v. selexipag administration in Period 2. • The time to reach maximum plasma concentration at

	steady-state ($t_{max, ss}$) of selexipag and its active metabolite, ACT-333679 after Uptravi (oral selexipag) in Period 1 and i.v. selexipag administration in Period 2. • Trough plasma concentration at steady state ($C_{trough, ss}$) of selexipag and its active metabolite, ACT-333679after Uptravi (oral selexipag) in Period 1 and i.v. selexipag administration in Period 2.
ASSESSMENTS	Refer to the schedule of assessments in Table 2.
STATISTICAL METHODOLOGY	Approximately 20 patients will be enrolled. In the GRIPHON Phase 3 pivotal study of selexipag, a proportion of 7.5% of patients on selexipag prematurely discontinued the study (i.e., without a morbidity/mortality event) due to prostacyclin-associated AEs. It is expected that the proportion of discontinuations will not be higher than 10%. The statistical analysis will be mainly descriptive, i.e., no hypotheses will be formally tested. Four analysis sets are defined in this study: • Screened Analysis Set includes all subjects who are screened and have a subject identification number. • i.v. Safety Set comprises all subjects who received at least one dose of i.v. study treatment. • Safety Set (SAF) includes all enrolled (included in the study on Day 1) subjects who receive at least one dose of selexipag (oral or i.v.). • Pharmacokinetic Analysis Set (PKS) comprises all subjects included in the SAF who received the 3 doses of i.v. study treatment and who complied with the protocol sufficiently and did not deviate from the protocol in a way that might affect the PK outcome of the study. The study comprises 3 main periods for analysis: Period 1, Period 2, and Period 3 and follow-up. AEs and SAEs will be tabulated, for the Safety Set and i.v. Safety Set, overall across periods as well as by study period. The proportion of discontinuations due to prostacyclin-associated AEs will be

	tabulated for the i.v. Safety Set and the SAF to address the primary objective. Due to the sample size, the proportion will be provided with a conservative 95% Clopper-Pearson confidence interval based on exact methods. All secondary safety endpoints will be listed and tabulated in Safety Set and i.v. Safety Set. Exposure will be summarized. ECG abnormalities and laboratory variables will be descriptively summarized, both longitudinally across the study periods as well as separately per period. Death will be summarized by cause, by period, and overall. The proportion of patients in each WHO FC (I , II , III and IV) will be tabulated at baseline and post-baseline, as well as the change in WHO FC at all assessed time points. Also the absence of worsening in WHO FC will be tabulated (i.e., patients that are either stable or improve).

PROTOCOL

1 BACKGROUND

Uptravi® (oral selexipag), a non-prostanoid, selective, prostacyclin receptor (IP receptor) agonist has recently been approved for pulmonary arterial hypertension (PAH) based on the demonstrated efficacy in a time to morbidity/mortality event study (AC-065A302/GRIPHON) [Sitbon 2015].

For patients with PAH treated with Uptravi, for whom a temporary interruption of Uptravi is unavoidable, and continuous treatment with selexipag is required, an intravenous (i.v.) formulation of selexipag has been developed.

1.1 Pulmonary arterial hypertension

PAH is a chronic, progressive and eventually fatal disease. PAH is characterized by pulmonary arterial vasoconstriction, vascular remodeling, inflammation, and fibrosis, resulting in a progressive increase in pulmonary arterial pressure and pulmonary vascular resistance, ultimately leading to ventricular failure and death [Barst 2004, D'Alonzo 1991, Galiè 2009, McLaughlin 2004].

The current management of PAH is based primarily on results from studies in adult patients, together with expert recommendations, such as those from the 5th World Symposium for PH, which were recently adopted by the European Society of Cardiology and European Respiratory Society [Galiè 2016]. It includes several treatment options, such as general measures (e.g., physical activity, infection prevention, birth control), supportive therapy (e.g., diuretics, oxygen, oral anticoagulants) and PAH-specific therapies. To date, there are several drugs targeting various therapeutic pathways approved for the treatment of PAH, including oral selexipag (Uptravi).

Current recommendations support the use of a combination of therapies and oral selexipag (Uptravi) is included in the treatment guidelines as an add-on to other oral treatments targeting the other pathways [Galiè 2016].

1.2 Study treatment: intravenous selexipag

1.2.1 Background information: selexipag

Selexipag is an IP receptor agonist. Enzymatic hydrolysis of selexipag by carboxylesterase 1 in the liver yields ACT-333679, the active metabolite, and major contributor to efficacy of selexipag in humans. ACT-333679 is approximately 37-fold more potent than selexipag in cellular systems, and is present at 3- to 4-fold higher levels than the parent drug at steady state in humans after oral selexipag administration. Selexipag and ACT-333679 induce an increase in intracellular cAMP concentrations upon stimulation of the IP receptor, leading to relaxation of vascular smooth muscle cells

and vasodilation of pulmonary arteries. The oral formulation of selexipag, under the brand name Uptravi, is approved for the treatment of patients with PAH. The i.v. formulation of selexipag tested in this study has been developed to be used in patients with PAH receiving Uptravi who would be temporarily unable to swallow tablets of Uptravi.

Refer to the Investigator's Brochure (IB) [Selexipag IB, Selexipag IB Amendment 1] for more detailed information.

1.2.2 Intravenous formulation

An i.v. formulation of selexipag, in the form of a dry powder to be reconstituted with sterile 0.9% NaCl solution, was developed. The inactive ingredients of this formulation are the following: sodium hydroxide, glycine, phosphoric acid and polysorbate 20.

1.2.3 Summary of nonclinical data

A comprehensive package of nonclinical *in vivo* and *in vitro* studies was performed that supported the approval of selexipag as oral treatment for PAH. Details of the nonclinical development of selexipag are described in the IB [Selexipag IB, Selexipag IB Amendment 1].

The local tolerance of i.v. selexipag at the concentration of 36 µg/mL (clinical formulation to achieve a dose of 1800 µg i.v. selexipag corresponding to plasma concentration obtained with 1600 µg of oral Uptravi) was tested following a single intravenous, paravenous or intramuscular administration to the New Zealand White rabbit. Clinical and injection site observations as well as body weight and food consumption were recorded daily for 4 days. Injection sites and surrounding tissues were examined histopathologically.

There were no clinical findings. Neither macroscopic nor microscopic observations indicated an effect of selexipag (36 µg/mL) at the injection sites.

1.2.4 Summary of clinical data

A comprehensive package of clinical studies was performed that supported the approval of selexipag as oral treatment for PAH. Details of the clinical development of selexipag oral formulation are described in the IB [Selexipag IB, Selexipag IB Amendment 1].

So far a different formulation of i.v. selexipag has been administered to 18 healthy male subjects in an absolute bioavailability study (AC-065-110) and has not been administered to subjects with PAH.

In the study AC-065-110, the geometric mean (95% confidence interval [CI]) of the area under the plasma concentration versus time curve (AUC) from 0 to infinity ($AUC_{0-\infty}$) of selexipag and ACT-333679 were 11.16 h·ng/mL (9.30, 13.38) and 14.91 h·ng/mL (11.42,

19.47), respectively, following a single i.v. infusion of 200 µg selexipag in healthy subjects. In the same study, following a single oral dose of 400 µg selexipag, geometric mean (95% CI) $AUC_{0-\infty}$ values of selexipag and ACT-333679 were 11.04 h·ng/mL (8.19, 14.87) and 37.97 h·ng/mL (30.18, 47.78), respectively. The exposure ($AUC_{0-\infty}$) to ACT-333679 was 1.34- and 3.44-fold higher than to selexipag after i.v. administration and oral administration, respectively. This difference in metabolite exposure is likely due to the first pass metabolism of oral selexipag [Selexipag IB, Selexipag IB Amendment 1].

Single doses of i.v. and oral selexipag were both well tolerated. The most frequently reported treatment-emergent adverse event (AE) was headache. All treatment-emergent AEs were of mild to moderate intensity. There were no serious adverse events (SAEs) and no AEs leading to discontinuation. No clinically significant treatment-emergent abnormality in clinical laboratory, vital signs, or ECG variables was observed.

1.3 Purpose and rationale of the study

1.3.1 Purpose of the study

This study aims to investigate whether i.v. selexipag, administered as a twice-daily (b.i.d.) infusion, is safe and well tolerated when subjects are temporarily switched from stable oral selexipag dose. This study will serve as the basis for regulatory filings for marketing authorization and will provide guidance to ensure a seamless switch from orally administered Uptravi to i.v. selexipag and return to Uptravi.

1.3.2 Rationale of the study

The development of an i.v. formulation of selexipag in PAH is guided by the understanding that in such a chronic, progressive, and ultimately fatal disease, treatment interruptions are to be avoided. The target population for an i.v. formulation of selexipag includes those PAH patients who are hospitalized (acutely or electively) and are unable to swallow tablets of Uptravi. Therefore, administration of i.v. selexipag would be appropriate for these patients to maintain selexipag plasma levels and to achieve comparable drug exposure to their oral dose of Uptravi. In the GRIPHON study, 9 selexipag-treated subjects were hospitalized and had their selexipag treatment temporarily interrupted for at least 3 days, indicating the usefulness of developing an i.v. formulation for selexipag.

1.4 Summary of known and potential risks and benefits

There is no direct individual benefit for the subject to participate in the study.

Uptravi local prescribing information essentially constitutes the benefit-risk summary for selexipag [Uptravi® USPI, Uptravi® SmPC]. The short and long-term safety profile of oral selexipag (Uptravi) has been established in the GRIPHON study and is mainly characterized by inter-individual susceptibility towards prostacyclin-associated AEs

associated with the mode of action of selexipag. Such AEs typically occur during the phase of individualized dose titration. No new safety findings were observed after single administration of i.v. selexipag in healthy subjects. Hence, the safety profile of i.v. selexipag is expected to be identical to that of Uptravi. Moreover, the dose of i.v. selexipag that will be administered during the study will target the same exposure to selexipag's active metabolite ACT-333679 as with their prescribed dose of Uptravi. Hence, the risks associated to study participation are expected to be limited to the ones associated with any i.v. administration of drugs and with the invasive study-specific procedures (i.e., repeated blood sampling for pharmacokinetic [PK] and safety assessments).

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

- Exclusion of subjects with unstable PAH condition or severe co-morbidities [see Section 4.4].
- In-patient hospitalization during pre-treatment and treatment periods (Period 1 and 2).
- Close monitoring of the subjects throughout the study, including frequent monitoring of vital signs following initiation of i.v. selexipag infusion.

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

2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective of this study is to assess whether temporary switching from a stable oral dose of selexipag to an i.v. dose of selexipag providing comparable exposure to active metabolite ACT-333679 and switching back to the initial oral dose of selexipag is safe and well tolerated in subjects with stable PAH.

2.2 Other objectives

- To evaluate the safety and tolerability of selexipag during each study period.
- To evaluate the PK of selexipag and its active metabolite, ACT-333679, at stable oral dose at steady state and after the switch from selexipag oral to selexipag i.v. in subjects with stable PAH.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multi-center, open-label, single-sequence, cross-over, Phase 3 study.

Approximately 20 subjects with stable PAH, currently treated with Uptravi at a stable dose (i.e., unchanged dose for at least 28 days), will be enrolled in order to obtain 18 evaluable subjects. Two different groups of subjects will be enrolled based on their dose of Uptravi:

- Group A: Subjects with a stable dose of Uptravi between 200 and 1000 µg b.i.d. (inclusive): at least 5 and up to 8 subjects will be enrolled in this dose group.
- Group B: Subjects with a stable dose of Uptravi between 1200 and 1600 µg b.i.d. (inclusive): At least 12 and up to 15 subjects will be enrolled in this dose group.

Subjects will be hospitalized during Period 1 and Period 2 [see Section 3.1.1].

The study will be conducted at approximately 10 sites in 2 countries. Subjects on a stable dose of Uptravi will be screened.

No interim analysis is planned.

3.1.1 Study periods

The study comprises the following consecutive periods:

Screening period:

Up to 28 days; starts with the signing of the Informed Consent Form (ICF) and ends with first day (Visit 2, Day 1) of Period 1 (Uptravi, pre-treatment period).

Treatment and observation period:

The treatment and observation period includes the following consecutive periods:

- Period 1 (Uptravi, pre-treatment period, in-hospital): 1 day
  Starts with intake of the morning dose of Uptravi at Visit 2 Day 1 and ends the following day, before initiation of the first infusion of i.v. selexipag.
- Period 2 (i.v. selexipag, treatment period, in-hospital): 36 hours (3 doses)
  Starts in the morning of Visit 2 on Day 2 with the start of the first infusion of i.v. selexipag and ends in the evening of Visit 2 on Day 3 before the evening administration of Uptravi. Note: oral administration of Uptravi is interrupted during the treatment period with i.v. selexipag.

- Period 3 (Uptravi, post-treatment period): 7 to 11 days
  Starts in the evening of Visit 2 Day 3 with the oral administration of Uptravi and ends 7 to 11 days later, at Visit 3.

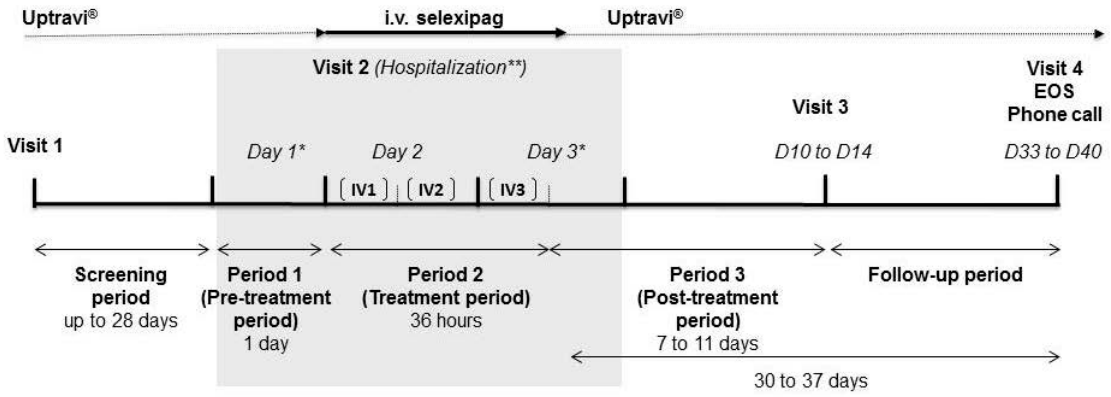
Safety Follow-up period:

Starts at the end of Visit 3 and ends 30 to 37 days after the last administration of i.v. selexipag with the End-of-Study (EOS) telephone call (Visit 4).

The visit schedule and protocol-mandated procedures will be performed according to the table of assessments [Table 2] and are described in Section 7.

The overall study design is depicted in Figure 1.

Figure 1 Study design



* 12-hour PK profile after the morning dose.
** For convenience hospitalization may be extended to the night before Day 1 and to the night of Day 3.
D = day; EOS = End-of-Study; IV1–IV3 = dose of i.v. selexipag; V = visit

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., signed ICF) and ends with the last EOS visit of the last subject. The duration of the study is expected to be approximately 9–12 months.

End-of-Study for a single subject is defined as the date of the EOS telephone call (Visit 4). If a subject withdraws consent, EOS is the date of consent withdrawal for this subject. If a subject is declared lost to follow-up [see also Section 8.2], EOS is the date of last successful contact for this subject.

For an individual subject, the study is completed with the EOS telephone call. The duration of the study for an individual subject will be up to 68 days (including a 36-h treatment period with i.v. selexipag).

3.2 Study design rationale

This study has been designed to address the question whether subjects with PAH on oral selexipag can be safely switched to i.v. selexipag and vice-versa. The single-sequence 3-period cross-over design has been chosen to mimic the intended clinical use of i.v. selexipag. The study plans to enroll approximately 20 subjects and will aim for at least 10 subjects to be treated with an i.v. selexipag dose corresponding to the oral dose of 1200–1600 µg b.i.d.

Subjects with a minimum of 28 days stable (i.e., dose unchanged) Uptravi dose will be enrolled. Subjects will be hospitalized and switched from the Uptravi oral dose to the corresponding b.i.d. i.v. dose of selexipag for a treatment period of 36 hours (3 doses) which allows the steady state of selexipag to be reached again and is therefore considered sufficient to assess tolerability and evaluate PK.

3.3 Study committees

No committees will be involved in the design or conduct of the study.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll male and female subjects diagnosed with Group 1 PAH [Galiè 2016], aged 18 to 75 years, who have been prescribed Uptravi (oral selexipag) as part of their standard treatment for PAH. Eligible subjects will be at a stable dose of Uptravi for at least 28 days prior to enrollment.

Subjects will be in WHO Functional Class (FC) I, II or III. They may be treated concurrently with a stable dose of diuretics or other PAH-specific medications which are not agonists of the IP receptor (i.e., ERA, PDE-5 inhibitors or sGC stimulators).

4.2 Rationale for the selection of the study population

The study population includes patients with PAH who have been prescribed Uptravi in compliance with local prescribing information (i.e., Uptravi® SmPC or Uptravi® USPI) as part of their standard treatment for PAH.

Stability of PAH-specific concomitant medications is an important pre-requisite to assess the safety and tolerability of the switch from Uptravi to i.v. selexipag. Therefore, patients who have been prescribed Uptravi and are currently treated at a stable dose are considered to represent an adequate study population to evaluate whether switching from

an oral dose of selexipag to a corresponding selexipag i.v. dose is well tolerated in subjects with stable PAH.

Subjects under 18 years are excluded due to absence of clinical experience and approval of selexipag for the treatment of pediatric patients. Subjects with significant cardiovascular, hepatic, or renal medical conditions are excluded since they could potentially be at greater risk of complications due to these pre-existing comorbidities, which could interfere with evaluation of study assessments and interpretation of study results.

4.3 Inclusion criteria

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

1. Signed ICF prior to any study-mandated procedure.
2. Male and female subjects at least 18 to 75 years inclusive.
3. Subjects with PAH belonging to the Updated Clinical Classification Group 1 [Galiè 2016]
4. Subjects who have been prescribed Uptravi in compliance with local prescribing information (i.e., SmPC or USPI).
5. Stable PAH defined as WHO FC I–III at Visit 1 and Visit 2 and no change (i.e., introduction or dose change) in PAH-specific medication (i.e., ERA, PDE-5 inhibitor or sGC stimulator) and diuretics in the last 28 days prior to Visit 2.
6. Subjects currently treated with Uptravi at a stable dose (i.e., unchanged dose) for at least 28 days before Visit 2.
7. A woman of childbearing potential is eligible only if she has a negative urine pregnancy test at Visit 1 and at Visit 2.

4.4 Exclusion criteria

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

1. Pregnant, planning to become pregnant or lactating.
2. Known and documented moderate or severe hepatic impairment.
3. Subjects having received gemfibrozil at any time since initiation of Uptravi.
4. Treatment with any prostacyclin and prostacyclin analogs within 28 days prior to Visit 1.
5. SBP < 90 mmHg at Visit 1 or at Visit 2.
6. Known or suspected uncontrolled hyperthyroidism.
7. Severe renal failure and ongoing or planned dialysis.

8. 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.
9. Known concomitant life-threatening disease with a life expectancy < 12 months.
10. Treatment with another investigational treatment within 3 months of Visit 1.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

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

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy,
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]),
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

The reason for not being of childbearing potential will be recorded in the Case Report Form (CRF).

4.5.2 Acceptable methods of contraception

Women of childbearing potential [see definition in Section 4.5.1] must continue following their local Uptravi® instructions (as indicated in USPI or SmPC, as applicable) with regard to use of methods of birth control from Screening (Visit 1) up to Visit 4.

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

5 TREATMENTS

5.1 Study treatment

5.1.1 Investigational treatment: description and rationale

Selexipag for i.v. administration will be supplied as 10 mL vials containing 1800 µg of dry powder of selexipag for injectable solution reconstitution.

The study treatment, i.v. selexipag, will be administered intravenously b.i.d. as an infusion over an 87-minute period [see Section 5.1.4]. The dose will be individualized for each subject and will correspond to subject's current dose of orally administered Uptravi.

Since selexipag's active metabolite ACT-333679 is up to 37-fold more potent than selexipag as an agonist of the human IP receptor in vitro, the i.v. formulation was

developed with the aim of reaching an exposure equivalent to the active metabolite (AUC between two doses) comparable to the one obtained with the oral formulation.

The correspondence between doses of Uptravi and i.v. selexipag doses were determined based on the results of the absolute bioavailability study (AC-065-110). The i.v. selexipag doses corresponding to the oral Uptravi doses are provided in Table 1.

Table 1 Correspondence of i.v. selexipag doses to Uptravi oral doses

Uptravi oral dose (µg)	Corresponding i.v. selexipag dose (µg)
200	225
400	450
600	675
800	900
1000	1125
1200	1350
1400	1575
1600	1800

5.1.2 Study treatment preparation

Before administration, the i.v. solution of selexipag is to be reconstituted and diluted with NaCl 0.9%.

Reconstitution and dilution of selexipag dry powder must be performed extemporaneously, followed by an immediate infusion. If necessary, the diluted solution can be kept in sterile conditions at 2–8 °C (35.6 °F and 46.4 °F) and be protected from light, for no longer than 4 hours before use. In such case, the solution is to be removed from the refrigerator approximately 15 minutes before use.

Residual vial contents must not be used for subsequent infusions.

The process for the preparation of the i.v. selexipag infusion solution is detailed in the Handling and Instruction for use of Investigational Medical Product Guidelines.

5.1.3 Infusion solution samples

For all subjects, infusion solution samples will be collected before each i.v. infusion and may be used to accurately confirm the amount of drug administered to each subject.

5.1.3.1 Procedures for sampling

Per subject, 1 aliquot of 1 mL must be obtained from the infusion solution for each infusion (i.e., a total of 3 aliquots per subject). The infusion solution samples will be collected from the tubing prior to the start of the infusion.

These aliquots must be kept in an amber vial and stored at (or below) −20 °C ± 5 °C (–4 °F ± 9 °F) in a freezer. To prevent degradation of selexipag in the infusion solution samples, exposure of the samples to light must be minimized.

The actual date and clock time of collection of each infusion solution sample must be entered in the CRF.

5.1.3.2 Shipping procedures

The central laboratory will ensure subsequent shipment of the infusion solution samples to the Analytical laboratory ([redacted]).

5.1.3.3 Bioanalysis

The analysis of the selexipag concentration in the infusion solution samples will be performed using a validated liquid chromatography with UV detector (LC-UV) assay.

Concentrations will be calculated by using an external reference standard. Quality control samples will be analyzed throughout the LC-UV assay. Their measured concentrations will be used to determine between-run and overall precision and accuracy of the analysis.

5.1.4 Study treatment administration

The following infusion scheme is to be followed:

- Start with an infusion rate of 20 mL/h (0.333 mL/min) for 15 min for the first 5 mL.
- Increase infusion rate to 37.5 mL/h (0.625 mL/min) for 72 min for infusion of the remaining 45 mL.

Note: A dedicated infusion line must be used for i.v. selexipag administration. No other drugs or solutions should be administered through this line.

The following information will be collected in the CRF to document each i.v. selexipag administration:

- Date of administration.
- Concentration of the i.v. infusion solution.
- For each infusion rate: clock time of start and end.

5.1.5 Treatment assignment

Approximately 20 subjects will be enrolled to perform the switch from stable dose of Uptravi to the corresponding dose of i.v. selexipag. The central Interactive Response

Technology (IRT) system will control enrollment in each group (5 to 8 subjects in Group A: 200–1000 µg b.i.d., and 12 to 15 subjects in Group B: 1200–1600 µg b.i.d.).

After verification that a subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT system at Visit 2 (Day 1, baseline). The IRT system will assign the treatment kit numbers.

5.1.6 Blinding

Not applicable.

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

Selexipag for i.v. administration is provided as a lyophilized sterile powder for solution for infusion, packaged in a 10 mL Type I clear borosilicate glass vial closed with a rubber stopper and a flip off cap. Each vial contains 1800 µg of selexipag and is packed in an individual box.

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

5.1.7.2 Study treatment distribution and storage

Study treatment supplies (dry powder vials) must be kept in their box and stored in an appropriate, secure area and stored according to the conditions specified on the label between 2 °C and 8 °C (35.6 °F and 46.4 °F) and protected from light.

5.1.7.3 Study treatment dispensing

Intravenous selexipag will be administered to the subject by site personnel according to the study-treatment preparation and administration procedures described in this protocol [see Sections 5.1.2 and 5.1.4]. The protocol-mandated study treatment administration procedures may not be altered without prior written approval from Actelion. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.7.4 Study treatment return and destruction

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

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

The inventory of study treatment dispensed (i.e., study treatment accountability) must be performed by site personnel and is to be recorded on the study-treatment dispensing and accountability log and in the CRF, and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the CRF will include at least the following information for each study treatment unit (i.e., selexipag dry powder vial) dispensed:

- Vial number
- Date dispensed
- Date returned

All study treatment supplies, including partially used or empty dry powder vials must be retained at the site for review by the CRA.

5.1.8.2 Study treatment compliance

Study treatment compliance is a measure of how closely the protocol instructions for administering i.v. selexipag were adhered to.

The compliance will be calculated as the percentage of the actual dose infused compared with the targeted dose to be infused.

Over the entire treatment period, compliance is expected to be between 80% and 120% otherwise it will be considered to be a protocol deviation and reported as such. The investigator must document in the subject's source notes the reasons for this protocol deviation.

5.1.9 Study treatment dose adjustments and interruptions

The i.v. selexipag dose corresponding to subject's stable Uptravi dose is expected to be fully infused each time and adjustment of i.v. selexipag dose is not allowed in this study.

Missing any of the 3 scheduled i.v. selexipag infusions is not allowed. If one or more of the i.v. selexipag infusions is missed, re-introduction is not permitted and i.v. selexipag treatment must be permanently discontinued [see Section 5.1.10]. Uptravi may be reintroduced after stopping i.v. selexipag, at the next scheduled dosing time point, if deemed medically needed for the subject.

5.1.10 Premature discontinuation of study treatment

A subject is considered as having prematurely discontinued study treatment if the third i.v. selexipag infusion was not initiated.

The decision to prematurely discontinue i.v. selexipag treatment may be made by the subject, the investigator or Actelion personnel. The main reason and whether discontinuation of i.v. selexipag treatment is the decision of the subject (e.g., tolerability- or efficacy-related), the investigator (e.g., due to pre-specified i.v. selexipag treatment discontinuation criteria, an AE or lack of efficacy), or Actelion (e.g., study terminated) must be documented in the CRF.

A subject has the right to discontinue i.v. selexipag treatment at any time, without any justification, by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study [see Section 8.2]). Although a subject is not obliged to provide his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

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

Study-specific criteria for discontinuation of i.v. selexipag treatment are described in Section 5.1.11.

A subject who prematurely discontinues i.v. selexipag treatment is to be discontinued from the study. For safety reasons, it is recommended to perform the assessments of Visit 3. The EOS telephone call (Visit 4) must be performed, provided that the subject's consent for this limited participation in the study has not been withdrawn. The assessments that are to be performed at each visit are described in Table 2.

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

5.1.11 Study-specific criteria for premature discontinuation of study treatment

Premature discontinuation of i.v. selexipag treatment

Treatment with i.v. selexipag must be stopped and its re-introduction is not to be considered in the following cases:

- New signs and symptoms of right heart failure following the switch to i.v. selexipag, indicating an acute worsening of the underlying PAH.
- Signs of pulmonary edema associated with confirmed diagnosis of pulmonary veno-occlusive disease.
- Symptomatic hypotension.
- Any missed infusion of i.v. selexipag.
- Need to initiate a forbidden medication (i.e., gemfibrozil, prostacyclin, prostacyclin analogs).

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing the ICF.

A therapy that is study-concomitant is any treatment that is ongoing or initiated after signing the ICF, or initiated up to 30 days after last i.v. selexipag infusion.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of first i.v. selexipag infusion or is initiated between the start of first i.v. selexipag infusion and the end of the last i.v. selexipag infusion.

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

5.2.2 Reporting of previous/concomitant therapy / auxiliary medicinal products in the CRF

The use of all study-concomitant therapy (including Uptravi, contraceptives, OTC drugs, traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the CRF. Previous therapies must be recorded in the CRF if discontinued less than 30 days prior to signing the ICF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, and indication will be recorded in the CRF.

5.2.3 Auxiliary medicinal products

The study population consists of subjects who have been prescribed Uptravi as part of their standard PAH treatment (i.e., Uptravi must not have been prescribed solely for the purpose of the study). Subjects will keep using Uptravi during their participation in the study as prescribed by their physician (i.e., same b.i.d. dose) and in compliance with the USPI/SmPC [Uptravi® SmPC; Uptravi® USPI] including the use of contraception for women of childbearing potential. Uptravi will be temporarily interrupted for 36 hours during the administration of study treatment (i.v. selexipag).

In addition to the standard information regarding concomitant medications, the following information regarding treatment with Uptravi will be recorded in the CRF:

- Dose of Uptravi and clock time of intake in the evening before Visit 2.
- Dose of Uptravi and clock time of intake in the morning and evening of Visit 2 Day 1.
- Dose of Uptravi and clock time of intake in the evening of Visit 2 Day 3.

5.2.4 Allowed concomitant therapy

PAH-specific therapies (i.e., ERA, PDE-5 inhibitor or sGC stimulator) are allowed if subjects have been on a stable dose for at least 28 days prior to Visit 2.

All other treatments considered necessary for the subject's well-being or required for contraception purposes and not categorized as forbidden concomitant medications are allowed during the study.

The dose of PAH medications (including diuretics) must be kept stable from Visit 1 (screening) and up to last PK blood sample collection on Visit 2 Day 3.

The dose of all other concomitant treatments should preferably be kept stable from Visit 1 (screening) and up to last PK blood sample collection on Visit 2 Day 3.

5.2.5 Forbidden concomitant therapy

- **Prostacyclin and prostacyclin analogs** are forbidden from Visit 1 (screening) until Visit 3, inclusive, to avoid concomitant administration of medications that would compete with selexipag as they have a similar mechanism of action.
- Concomitant administration of **gemfibrozil** affects the PK of selexipag and ACT-333679. Therefore it is prohibited from Visit 1 (screening) and up to EOS telephone call (Visit 4), inclusive.

- Concomitant administration of **any other investigational drug** is prohibited from Visit 1 (screening) and up to EOS telephone call (Visit 4), inclusive, as it may interfere with assessment of safety and tolerability of i.v. selexipag.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

Not applicable. No efficacy endpoint for this safety and tolerability study.

6.2 Safety and tolerability endpoints

6.2.1 Definitions

Prostacyclin-associated AEs and PAH-related AEs will be defined by Preferred Term in the Statistical Analysis Plan (SAP).

6.2.2 Main safety and tolerability endpoints

The main safety and tolerability endpoints will be analyzed over Period 1, Period 2, and Period 3 and follow-up period combined.

- Discontinuations due to prostacyclin-associated AEs.
- AEs and SAEs.
- Prostacyclin-associated AEs.
- AEs related to injection site reactions.
- PAH-related AEs.

6.2.3 Other safety and tolerability endpoints

The other safety and tolerability endpoints will be analyzed:

- For each study period separately: Period 1; Period 2; Period 3 and follow-up period combined.
- For Period 1 and Period 2 combined.
- For Period 2 and Period 3 combined.

The following endpoints will be analyzed:

- Discontinuations due to prostacyclin-associated AEs.
- Discontinuations due to any AEs.
- AEs and SAEs.
- Prostacyclin-associated AEs.
- PAH-related AEs.

- Change from baseline in vital signs (SBP, diastolic blood pressure [DBP], and pulse rate) and body weight.
- ECG abnormalities.
- Marked laboratory abnormalities (MLAs).
- Change from baseline in WHO FC.

6.3 Pharmacokinetic endpoints

- The AUC during a dose interval at steady state ($AUC_{\tau, ss}$) of selexipag and its active metabolite, ACT-333679, after Uptravi (oral selexipag) in Period 1 and after i.v. selexipag administration in Period 2.
- The maximum plasma concentration at steady state ($C_{max, ss}$) of selexipag and its active metabolite, ACT-333679, after Uptravi (oral selexipag) in Period 1 and i.v. selexipag administration in Period 2.
- The time to reach maximum plasma concentration at steady state ($t_{max, ss}$) of selexipag and its active metabolite, ACT-333679, after Uptravi (oral selexipag) in Period 1 and i.v. selexipag administration in Period 2.
- Trough plasma concentration at steady state ($C_{trough, ss}$) of selexipag and its active metabolite, ACT-333679, after Uptravi (oral selexipag) in Period 1 and i.v. selexipag administration in Period 2.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 2. For all visits, the subjects must be seen on the designated day or within the visit window defined in Table 2. A follow-up safety visit must be performed by telephone 30 to 37 days after administration of the last i.v. dose of study treatment.

In the event of premature discontinuation of study treatment, it is recommended to perform the assessments of Visit 3. The EOS telephone call (Visit 4) must be performed, provided that the subject's consent for this limited participation in the study has not been withdrawn.

Subjects who prematurely discontinue study treatment for any reason will not be replaced.

7.1.1 Screening/re-screening

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

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

Subjects who are in screening when the enrollment target is met will not be enrolled.

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication). All screening assessments do not need to be repeated at the time of re-screening if they were performed within 28 days.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator. Only the results from study-specific assessments [as listed in Section 7.2], 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.

Table 2 Visit and assessment schedule

PERIODS	Name	SCREENING	TREATMENT AND OBSERVATION PERIOD				FOLLOW-UP
			Period 1 (Pre-treatment Period; Uptravi)	Period 2 (Treatment Period; i.v. selexipag)		Period 3 (Post-treatment Period; Uptravi)	
VISITS[1]	Number	Visit 1	Visit 2			Visit 3	Visit 4 (Phone call)
	Name	Screening	Baseline				EOS
	Time	Day –28 to Day –1	Day 1	Day 2 IV-1 (AM)	Day 2 IV-2 (PM)	Day 3 IV-3 (AM)	Day 12 (± 2days)	30 to 37 days after i.v. study treatment discontinuation
Informed consent		X						
Eligibility		X	X					
Demographics / Medical history		X						
WHO FC		X	X			X[2]	X	
Previous/concomitant therapy		X	X	X	X	X	X	X
Physical examination		X					X	
Vital signs (BP, pulse rate)		X	X	X[5]		X[5]	X	
Body weight and Height[3]		X	X			X	X	
Hospitalization[4]**			⟷					
Laboratory tests*		X	X[6]			X	X	
12-lead ECG*			X	X[7]	X[7]	X[7]	X	
Urine pregnancy test**		X	X					X
PK sampling[8]			X			X		
Study treatment administration (i.v. selexipag)				X	X	X		
Infusion solution sampling[9]				X	X	X		
SAEs/AEs[10]		X	X	X	X	X	X	X

AE = adverse event; BP = blood pressure; ECG = electrocardiogram; EOS = End-of-Study; FC = Functional Class; i.v. = intravenous; PK = pharmacokinetic; SAE = serious adverse event; WHO = World Health Organization. [*]Electronically transferred to sponsor. [**] Assessment not collected in CRF

[1.] Unscheduled visits may be performed at any time during the study. Assessments performed during unscheduled visits are at the discretion of the investigator.
[2.] On Day 3, WHO FC is to be assessed at the end of the i.v. selexipag infusion.
[3.] Height will be assessed at Visit 1 (screening) only.
[4.] In-patient hospitalization of subjects is mandatory during Visit 2 (Period 1 and Period 2) (i.e., 2 overnight stays from Day 1 to Day 3). For convenience, the hospitalization may be extended to the night before Day 1 and to the night of Day 3.
[5.] Vital signs (BP and pulse rate) will be assessed at 7 different time points as detailed in Table 3.
[6.] If Visit 1 and Visit 2 Day 1 are performed within 7 days, laboratory tests do not have to be repeated at Visit 2 Day 1.
[7.] ECG will be performed at pre-dose and within 30 minutes after stopping of infusion (i.v. selexipag).
[8.] PK profile includes 7 blood samples. Timing of blood samples is detailed in Table 3
[9.] Infusion solution samples will be taken from the tubing before each infusion [see Table 3].
[10.] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after i.v. selexipag study treatment discontinuation must be reported.

Table 3 Visit 2 vital signs and PK blood collection schedule

	Visit 2 (hospitalization)																					
	Period 1 (Uptravi, Pre-treatment Period)							**Period 2 (Treatment Period; i.v. selexipag)**														**Period 3 (Uptravi, Post-treatment Period)**
	Day 1							**Day 2**							**Day 3**							
Time[1] after morning dose	0 h	1 h	2 h	4 h	6 h	8 h	12 h	0 h	25 min	87 min	4 h	6 h	8 h	12 h	0 h	25 min	87 min	4 h	6 h	8 h	12 h	
Uptravi oral intake	X						X														X	
Infusion solution sample[2]								X						X	X							
Selexipag i.v. infusion								X →						X[5]	X →							
PK blood sample	X[3]	X	X	X	X	X	X[3]								X[3]	X	X[4]	X	X	X	X[3]	
Vital signs (pulse rate and BP)	X							X[3]	X	X[4]	X	X	X	X[3]	X[3]	X	X[4]	X	X	X	X[3]	

BP = blood pressure; i.v. = intravenous; PK = pharmacokinetic.

[1] A time window of ± 5% is allowed for PK time points.
[2] Infusion solution sample will be taken from the tubing prior to selexipag infusion.
[3] Vital signs and PK blood sample must be assessed/taken before selexipag administration (oral or i.v.).
[4] Immediately before stopping the infusion.
[5] Evening i.v. selexipag infusion to be started 12 h ± 1 h after the start of the morning infusion.

7.2 Study assessments

The study assessments are listed in Table 2 and Table 3. The assessments that are mandatory during a visit are marked with an 'X'.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel) and are recorded in the CRF, unless otherwise specified. Results for study-specific assessments performed during unscheduled visits will also be recorded in the CRF. The following order of assessments must be followed:

- When blood pressure and PK blood sampling are to be assessed at the same time point, blood pressure measurements will be performed before PK sampling.

If the Principal Investigator (PI) delegates any study procedure/assessment for a subject to an external facility, he/she must inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains the responsibility of the PI.

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

Equipment for which calibration certificates / evidence of maintenance are needed:

- Temperature measurement devices for selexipag dry powder vials storage area, plasma PK sample and infusion solution sample storage area.
- ECG equipment.
- Infusion pump.
- Cooling centrifuge used for preparation of plasma PK samples.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, and ethnicity (if allowed in the country). Relevant medical history/current medical conditions (e.g., chronic and ongoing acute conditions, serious past conditions) present before signing the ICF will be recorded on the medical history CRF form. Where possible, diagnoses and not symptoms will be recorded.

Medical history of special interest will be captured on the specific Medical History CRF form and includes:

- Etiology of PAH.
- Date of initial diagnosis.
- Uptravi dose at screening.

For subjects who failed screening, at least the following data will be recorded in the CRF if available:

- Demographics.
- Inclusion criteria not met and exclusion criteria met.
- Medical history of special interest.
- Central laboratory and ECG results will be transferred to the sponsor if available.
- all AEs and SAEs.

7.2.2 Efficacy assessments

Not applicable.

7.2.3 Safety assessments

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

7.2.3.1 Physical examination

Physical examination will be performed according to standard practice at site and guided by medical history and/or symptoms.

Information for all physical examinations must be included in the source documentation at the study site. The observations will be reported according to body system in the CRF as either normal or abnormal. Any abnormality must be specified on the corresponding CRF form, describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings (other than those related to PAH) that are present prior to signing the ICF must be recorded on the Medical History CRF form. Physical examination findings made after signing the ICF which meet the definition of an AE [see Section 9.1.1] must be recorded on the AE form of the CRF.

7.2.3.2 Vital signs

Pulse rate, SBP, and DBP will always be measured in a supine position and will be recorded in the CRF. It is recommended to assess vital signs on the same arm throughout the study and to allow the subject to rest for at least 5 minutes prior to each measurement.

During the i.v. selexipag treatment (Period 2), vital signs will be measured before start of the morning infusion of selexipag and 6 times after the start of infusion (time schedule of measurements is detailed in Table 3). On Day 3, vital signs will be measured on the arm where the line for PK sample collection is placed (opposite arm from infusion of selexipag) and vital signs are to be measured immediately prior to blood collection.

7.2.3.3 Weight and height

Body weight will be measured in indoor clothing but without shoes and recorded in the CRF.

Height will be measured without shoes and recorded in the CRF.

7.2.3.4 ECG assessment

Standard 12-lead ECGs will be recorded with the subject in a fully rested supine position. Prior to the measurement it is recommended to allow the subject to rest for at least 5 minutes.

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

Central ECG reports will be sent to the investigator. In the event of specific (pre-defined in the central ECG laboratory manual) ECG abnormalities, the central ECG laboratory will alert Actelion personnel and the concerned site personnel.

All ECG reports must be reviewed, signed, and dated by the investigator or delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the ECG report whether abnormal values or findings are considered clinically relevant or not.

Clinically relevant ECG findings that are known at the time of signing the ICF must be documented in the Medical History section of the CRF.

Clinically relevant ECG abnormalities detected after signing the ICF must be reported as an AE or SAE as appropriate.

The data records will be electronically transmitted to the central ECG laboratory for central reading. ECG data will be electronically transferred from the ECG laboratory database to Actelion. Details on ECG procedures (recording, transfer of data, and reporting) will be provided in the central ECG laboratory manual.

The following variables will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms) and any ECG findings. QTc (ms) will be calculated according to Bazett's and Fridericia's formulae (i.e., $QTcB = QT/\sqrt{(RR)}$ and $QTcF = QT/(RR)^{1/3}$).

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

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

Exceptional circumstances that will require recording of local laboratory results of the variables described in Section 7.2.4.2 (with corresponding normal ranges) include hospitalization of the subject due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If a central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator will consider collecting an additional sample as soon as possible if deemed medically needed for repeat analysis.

Central laboratory reports will be sent to the investigator. In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion personnel and the concerned site personnel. Alert flags that will trigger such notifications are displayed in Appendix 1.

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

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

7.2.4.2 Laboratory tests

<u>Hematology</u>

- Hemoglobin (g/L)
- Hematocrit (L/L)
- Erythrocytes (10^{12}/L)
- Leukocytes with differential counts (10^{9}/L)
- Platelets (10^{9}/L)

Clinical chemistry

- Alanine aminotransferase (U/L)
- Aspartate aminotransferase (U/L)
- Alkaline phosphatase (U/L)
- Total and direct bilirubin (µmol/L)
- Creatinine (µmol/L)
- Sodium, potassium (mmol/L)

Pregnancy test

Only for women of childbearing potential:

- Urine pregnancy test will be performed as standard assessment during this study.
- If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

The results of the pregnancy tests will not be collected in the CRF.

7.2.5 Pharmacokinetic assessments

7.2.5.1 Pharmacokinetic assessments

PK blood samples will be collected for all subjects in order to establish a 12-hour PK profile at steady state for selexipag and ACT-333679 when subjects are at their stable dose of Uptravi and after the switch from Uptravi to i.v. selexipag.

7.2.5.1.1 Timing for sampling

For all subjects, a total of 14 blood samples will be drawn.

PK blood samples will be collected as displayed in Table 3.

On Day 1, plasma concentrations of selexipag and ACT-333679 will be measured at pre-dose (trough) and 1, 2, 4, 6, 8, and 12 hours after the morning dose of Uptravi.

On Day 3, plasma concentrations of selexipag and ACT-333679 will be measured at pre-dose (trough) and 25 min, 87 min (i.e., immediately before stopping the infusion), 4, 6, 8, and 12 hours after initiation of the morning i.v. infusion of selexipag.

The allowed time window is ± 5% from the scheduled time point (refer to laboratory manual for conversion table between % and minutes).

7.2.5.1.2 Procedures for sampling

Detailed instructions for the collection, preparation, labeling, storage, and shipment of the plasma samples can be found in the laboratory manual provided to the investigator.

Important points:

- Trough blood samples must be drawn before the morning dose of selexipag (oral or i.v.) is administered.
- 12-hour PK blood samples must be drawn before the evening dose of Uptravi is administered.
- PK blood samples on Day 3 must be taken from the opposite arm of infusion of i.v. selexipag, i.e., do not use the same arm for i.v. selexipag infusion and PK sampling.
- To prevent degradation of selexipag and ACT-333679 in the PK samples, exposure of the PK samples to light needs to be minimized.

The actual date and clock times of each PK blood sampling must be collected in the CRF.

7.2.5.1.3 Bioanalysis

The plasma concentrations of selexipag and ACT-333679 will be determined using a validated LC-MS/MS assay. The limit of quantification (LOQ) for both analytes in plasma is 0.01 ng/mL. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be used to determine between-run and overall precision and accuracy of the analysis. No genetic analysis will be conducted.

7.2.5.1.4 Shipping procedures

The site staff will be responsible for the shipment of the plasma PK samples. Samples must be sent to the central laboratory ([redacted]), at time intervals as defined in the laboratory manual. The samples, together with the completed shipment forms, must be packed securely in polystyrene-insulated shipping containers containing enough dry ice to last for 48 h. The central laboratory will ensure subsequent shipment of the plasma PK samples to [redacted] Actelion.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion

A subject who received at least one dose of i.v. treatment and performed the follow-up period is considered to have completed the study.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the CRF

from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted in case the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts, and enter the loss of follow-up information into the CRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

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

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

8.3 Premature termination or suspension of the study

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

If the study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the independent ethics committees / institutional review boards (IECs/IRBs), and health authorities, as appropriate, and provide the reasons for the suspension or termination.

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

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

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

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

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations. Such care may include continuation of their prescribed Uptravi.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse events

9.1.1 Definition of adverse events

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

A treatment-emergent AE is any AE temporally associated with the use of i.v. selexipag; from start of first i.v. selexipag infusion until 30 days after end of last i.v. selexipag infusion (i.e., Period 2, and Period 3 and follow-up Period combined); whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.

- Continuous persistent disease or symptoms present at study start that worsen following the signing of informed consent.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse, abuse of the study treatment (i.v. selexipag) and study treatment errors will be reported as an AE.

Overdose is defined as any infused dose of selexipag greater than the dose corresponding to 1600 µg b.i.d. of Uptravi.

Study treatment errors include medication error (e.g., any infused dose of selexipag greater than the individual corresponding prescribed dose of Uptravi) and administration errors (e.g., incorrect infusion rate).

9.1.2 Intensity of adverse events

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

If an AE changes in intensity (i.e., worsening or improvement) during the course of the study, this will be reported in the CRF.

The three categories of intensity are defined as follows:

- **Mild**

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

- **Moderate**

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

- **Severe**

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

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

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

9.1.3 Relationship to study treatment

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

9.1.4 Reporting of adverse events

All AEs with an onset date after signing of informed consent and up to 30 days after study treatment discontinuation (i.e., EOS visit / telephone call) must be recorded on specific AE form of the CRF.

Reporting of AE in CRF will include onset time.

9.1.5 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up information obtained after the subject's EOS visit / telephone call will not be collected by Actelion.

9.2 Serious adverse events

9.2.1 Definitions of serious adverse events

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

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

subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

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

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

9.2.2 Reporting of serious adverse events

All SAEs occurring after signing of informed consent up to 30 days after study treatment discontinuation must be reported on AE forms in the CRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment (i.v. selexipag) or study-mandated procedures.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures.

9.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after study treatment discontinuation must be followed up until resolution or stabilization, or until the event outcome is provided. The follow-up information obtained after the subject's EOS visit / telephone call must be reported to Actelion Global Drug Safety, but it is not recorded in the CRF.

9.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to Actelion Global Drug Safety (contact details are provided on the SAE form) within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.2.5 Reporting procedures

All SAEs must be reported by the investigator to Actelion Global Drug Safety within 24 hours of the investigator's first knowledge of the event.

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

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

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

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

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

The expectedness of a reported serious adverse reaction is determined by Actelion in the reference safety information (RSI) section provided in the most recent version of the IB. Any SAE that is reported as related and assessed as unexpected against the RSI will be classified as a suspected unexpected serious adverse reaction (SUSAR) and reported by Actelion to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

The following SAEs are commonly seen in subjects with underlying PAH disease and are therefore anticipated to occur in this subject population. These SAEs (unless fatal) do not require expedited reporting to health authorities, ECs/IRBs, and investigators: 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. Like all other SAEs, these SAEs must be reported on a 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 form of the CRF.

9.3 Pregnancy

If a woman becomes pregnant during the study, the investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.3.1 Reporting of pregnancy

Any pregnancy occurring after study start (i.e., signing of informed consent) up to 30 days following study treatment 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 Actelion Global Drug Safety [see contact details provided on the Pregnancy form], and on an AE form in the CRF.

9.3.2 Follow-up of pregnancy

Any pregnancies must be followed-up to their conclusion and the outcome must be reported to Actelion Global Drug Safety.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE forms in the CRF. Any SAE occurring during the pregnancy must be reported on a SAE form as described in Section 9.2.1.

9.4 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the Actelion Clinical Team (in charge of ensuring subjects' safety as well as data quality).

10 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by a designated Contract Research Organization (CRO) supervised by Actelion.

A SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

10.1 Analysis sets

10.1.1 Screened Analysis Set

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

10.1.2 Full Analysis Set

Not applicable.

10.1.3 i.v. Safety Set

The i.v. Safety Set comprises all subjects who received at least one dose of i.v. study treatment.

The i.v. Safety Set will be used to capture safety and tolerability for all subjects who had at least one dose of i.v. selexipag.

All analyses for Periods 2 and 3 combined, and for Period 2 separately will be carried out on the i.v. Safety Set.

10.1.4 Safety Set

The Safety Set (SAF) includes all enrolled (included in the study on Day 1) subjects who receive at least one dose of selexipag (oral or i.v.).

10.1.5 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKS) comprises all subjects included in the SAF who received the 3 doses of i.v. study treatment and who complied with the protocol sufficiently and did not deviate from the protocol in a way that might affect the PK outcome of the study. Criteria for sufficient compliance include exposure to treatment, availability of measurements, and absence of major protocol deviations that have an impact on the PK. The full list of criteria will be detailed in the SAP.

10.1.6 Usage of the analysis sets

Subject disposition is described for the Screened Analysis Set. Demographics and baseline characteristics will be reported on the SAF. Safety analyses will be carried out on the SAF and on the i.v. Safety Set. PK analyses will be carried out on the PKS. Subject listings are based on the SAF or Screened Analysis Set as applicable. The following table describes the use of the analysis sets.

Table 4 Reporting periods and corresponding analysis sets.

Reporting period(s)*	Variables	Analysis set
Period 1	Safety and tolerability	SAF
Period 2	Safety and tolerability	i.v. Safety Set
Period 3	Safety and tolerability	i.v. Safety Set
Period 1 and 2	Safety and tolerability	SAF
Period 2 and 3	Safety and tolerability	i.v. Safety Set
Period 1 and 2 and 3	Safety and tolerability	SAF
Period 1 and 2	Pharmacokinetic	SAF, PKS

Follow-up period will be reported together with Period 3.
* If a subject does not take at least one dose of selexipag i.v. they will not be considered as having entered Period 2 (or 3).

10.2 Variables

All analyses will be mainly descriptive in nature.

10.2.1 Primary efficacy variable(s)

No primary efficacy endpoint is defined for this study. Tolerability endpoints address the main objective.

10.2.2 Key secondary efficacy variables

Not applicable.

10.2.3 Safety variables

The following variable will be derived from the safety endpoints:

- Proportion of AEs
- Proportion of prostacyclin-associated AEs
- Proportion of AEs related to injection site reactions
- Proportion of PAH-related AEs
- Proportion of SAEs
- Proportion of AEs leading to discontinuation
- Proportion of discontinuations due to prostacyclin-associated AEs
- Proportion of ECG abnormalities
- Proportion of MLAs
- Change in WHO FC.

Other safety variables will be taken into account such as, e.g., changes in vital signs and body weight.

10.2.3.1 Adverse events

An AE is defined as any event that is recorded on the AE CRF module regardless of the onset date. The onset date will determine which events belong to each of the treatment periods (i.e., before/after intake of oral/i.v. selexipag). All events during the study will be listed and/or tabulated accordingly. In the event of partially missing dates/times, imputation will be carried out to link event and period using a conservative algorithm.

10.2.3.2 Laboratory data

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

10.2.3.3 ECG

ECG analyses are based on data received from the central ECG. All transferred central ECG data are taken into account regardless of whether they correspond to scheduled or unscheduled assessments.

Baseline ECG refers to the latest ECG performed prior to the start of study treatment.

All ECG values collected will be listed. Descriptive summary statistics of each variable (HR and the intervals PR, QRS, QT, QTcF and QTcB) by visit will be provided for observed values and absolute changes from baseline.

10.2.4 Pharmacokinetic variables

Plasma PK parameters of selexipag and its active metabolite, ACT-333679, will be derived by non-compartmental analysis of the concentration-time profiles. The PK parameters will be calculated on the basis of the real blood sampling time points (in relation to the last selexipag intake during each period).

The measured individual plasma concentrations of selexipag will be used to directly obtain $C_{trough,\ ss}$, $C_{max,\ ss}$, and $t_{max,\ ss}$.

$AUC_{\tau,\ ss}$ will be calculated according to the linear trapezoidal rule using the measured concentration-time values above the LOQ during one dosing interval at steady state.

For mean value calculations, all values below the limit of quantification (BLQ) will be set to zero. If > 50% of the values at a given time point are BLQ, no mean value will be calculated. Mean concentration-time profiles will be generated using these criteria.

$C_{max,\ ss}$, $C_{trough,\ ss}$, and $AUC_{\tau,\ ss}$, values are assumed to be log-normally distributed [Julious 2000].

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

The statistical analysis will be mainly descriptive, i.e., no hypotheses will be formally tested. CIs will be calculated at the 95% level for the main safety variables, per period (and combination of periods) and overall. CIs for PK variables will be calculated at the 95% level for descriptive analysis. A level of 90% will be used for the ratio of geometric means of PK parameters to account for the limited sample size.

10.3.2 Analysis of the primary efficacy variable(s)

Not applicable.

10.3.3 Analysis of key secondary efficacy variable(s)

Not applicable.

10.3.4 Analysis of the safety variable(s)

The study comprises 3 main periods for analysis, Period 1 (Uptravi, pre-treatment), Period 2 (i.v. selexipag; treatment period) and Period 3 (Uptravi; post-treatment).

Tolerability and safety analyses will be carried out descriptively on the SAF and the i.v. Safety Set. AEs that occur prior to first intake of Uptravi on Day 1 as a result of study-mandated procedures will be analyzed descriptively in the Screened Analysis Set. All AEs and SAEs will be coded using MedDRA.

The number and percentage of subjects experiencing AEs by period [as per Table 4] will be tabulated by MedDRA System Organ Class (SOC) and individual Preferred Term (PT) within each of the SOCs, in descending order of incidence of SOC, alphabetical order of PT, PT descending order of incidence and alphabetical order of PT for each period separately. AEs and SAEs will be tabulated, for the SAF and i.v. Safety Set overall across periods as well as by study period. The same summary applies to SAEs, AEs leading to premature discontinuation of study treatment and death. Furthermore, AEs and SAEs will be tabulated by severity and relationship to i.v. selexipag.

The proportion of discontinuations due to prostacyclin-associated AEs and AEs leading to discontinuation will be tabulated for the SAF and i.v. Safety Set (as well as all other discontinuations, irrespective of reason). Due to the small sample size, estimates of the proportion will be provided with a conservative 95% Clopper-Pearson CI based on exact methods.

Safety endpoints will be listed and tabulated in the SAF and i.v. Safety Set, overall and by study period [see Table 4 for details]. Treatment exposure will be summarized. Selexipag dose (oral and i.v.) will be summarized by visit, number of subjects and percentage. Shift tables between oral and i.v. dose will also be provided.

ECG abnormalities and laboratory variables will be descriptively summarized, both longitudinally across the study periods as well as separately per period. Death will be summarized by cause, by period, and overall.

All laboratory test assessments will be listed by subject, for all subjects in the SAF and will be tabulated on the SAF and i.v. Safety Set. Descriptive summary statistics by visit will be provided for observed values and absolute changes from baseline.

10.3.5 Analysis of PK variables

For all PK analyses, the Pharmacokinetic Analysis Set will be employed.

- Plasma concentrations of selexipag and ACT-333679 will be summarized per time point by dose and period using arithmetic mean, geometric mean, minimum, median,

maximum, standard deviation (SD), standard error (SE), and two-sided 95% CI of the means.

- $C_{trough, ss}$ of selexipag and ACT-333679 will be listed by dose, period and subject, and will be summarized by dose and period using arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, and coefficients of variation (CV, CV_{ln}) in %, and two-sided 95% CI of the means.

- $C_{max, ss}$, $t_{max, ss}$, and $AUC_{\tau, ss}$ of selexipag and ACT-333679 will be listed by dose, period, and subject.

- $C_{max, ss}$, $t_{max, ss}$,* and $AUC_{\tau, ss}$, will be summarized by dose and period with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, CV% and CV_{ln}%, 95% CI of the arithmetic and geometric means, and inter-subject coefficient of variation (CV_b). (* For $t_{max, ss}$, the geometric mean, its 95% CI and CV_{ln} will not be calculated).

- Differences in $C_{max, ss}$ and $AUC_{\tau, ss,}$ of selexipag and ACT-333679 between periods will be explored after dose normalization and within each dose level by using the 90% CI of the ratio of the geometric means of selexipag i.v. (test treatment) versus selexipag oral (reference treatment). The log-transformed values will be analyzed by mixed-effect models including treatment and period as fixed effects and subject as random effect. The ratios of geometric means and their 90% CI will be calculated from the corresponding back log-transformed contrasts of the mixed-effects models for $C_{max, ss}$ and $AUC_{\tau, ss}$ of selexipag and ACT-333679 after oral or i.v. selexipag administration.

- Differences for $t_{max, ss}$ of ACT-333679 between periods will be explored within each dose level using the Wilcoxon signed rank test providing the median differences and their 90% CI.

- Dose proportionality for $AUC_{\tau, ss,}$ of selexipag and ACT-333679 after selexipag i.v. will be explored by the power model as described by [Gough 1995], (this analysis will only be done if there are at least 3 different doses in the study).

- $C_{max, ss}$ and $AUC_{\tau, ss}$ ratio of ACT-333679 / selexipag will be listed by dose, period, and subject and will be summarized by dose and period.

10.3.6 Analysis of other variables

The proportion of subjects in each WHO FC (I, II, III and IV) will be tabulated at baseline and post-baseline, as well as the change in WHO FC at all assessed time points. Also the absence of worsening in WHO FC will be tabulated (i.e., subjects that are either stable or improved). A shift table approach may also be used.

10.4 Interim analyses

No interim analysis is planned for this study.

10.5 Sample size

Approximately 20 subjects will be enrolled to have at least 18 subjects in the i.v. Safety Set. In the GRIPHON Phase 3 pivotal study of selexipag, a proportion of 7.5% of subjects prematurely discontinued the study (i.e., without a morbidity/mortality event) due to prostacyclin-associated AEs across the titration and maintenance phases. It is expected that the proportion of early discontinuations during the entire study will not be higher than 10% (i.e., that approximately 18 subjects will enter the i.v. period).

A sample size of 18 subjects in the i.v. Safety Set will assure, if the true rate of discontinuations due to prostacyclin-associated AEs (p_0) is between 5% and 10%, that the half-width (ω) of the 95% CI will be below 35%.

The precision achieved with a sample size of approximately 18 subjects in the i.v. Safety Set is considered adequate for this study (e.g., the upper bound of the CIs for the i.v. Safety Set excludes values above 35% and for the SAF above 32%).

11 DATA HANDLING

11.1 Data collection

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

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

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

For each subject screened, regardless of study treatment initiation, a CRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF.

11.2 Maintenance of data confidentiality

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

11.3 Database management and quality control

CRFs will be used for all subjects. The investigators will have access to the site CRF data until the database is closed. Thereafter, they will have read-only access. The CRF must be kept current to reflect subject status at any time point during the course of the study.

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

This process will continue until database closure.

Laboratory samples and ECG readings will be processed through a central vendor and the results will be electronically sent to Actelion.

AEs are coded according to the latest version of MedDRA used by Actelion.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate Actelion Quality System docs. After database closure, the investigator will receive the CRFs of the subjects of his/her site (including all data changes made) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

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

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

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

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

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

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject and/or legally designated representative to consider his or her decision to participate in the study and it shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

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

Site personnel authorized to participate in the consent process and/or to obtain consent from the subject will be listed on the Delegation of Authority form supplied by Actelion. A study physician must always be involved in the consent process.

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

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

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

12.4 Indemnification, compensation and expenses to subjects and investigators

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

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

There is no direct individual medical benefit for the subject to participate in the study. In addition to the refund for the study-related expenses (e.g., travel costs, meals, hotel…), the subject will be offered financial compensation for their participation to the study in compliance with applicable local regulations.

12.5 Protocol adherence/compliance

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

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH-GCP must be reported to the IEC/IRB and regulatory authorities according to Actelion or (overruling) local requirements.

All protocol deviations will be reported in the Clinical Study Report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

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

12.7 Essential documents and retention of documents

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

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

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

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

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The print-outs must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed either with the subject's medical records or with the subject's CRF.

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

12.8 Monitoring

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

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

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

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the CRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, verification

of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data-collection times.

The PI must ensure that the CRF is completed after a subject's visit (site visit or telephone call), and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

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

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

12.9 Investigator Site File

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

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

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

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

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

12.10 Audit

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

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

12.11 Inspections

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

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

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

12.12 Reporting of study results and publication

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

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

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

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

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

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

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

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

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14 APPENDICES

Appendix 1 Marked laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for "low", H for "high".

The term "marked abnormality" describes laboratory values, with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the CTCAE grading system [CTCAE 2010] [see Table 5].

The marked abnormal values (i.e., LL, LLL, HH, HHH) will also be used as flags and alerts on the laboratory reports to the investigators, and Actelion:

- Marked abnormality HH/LL: flag on laboratory report to investigators.
- Extreme marked abnormality HHH/LLL: alert on laboratory report to investigators and subject to additional communication to investigator via telephone call and to Actelion via email.

Thresholds for abnormality of level L or H are not provided in this appendix but will be provided in the central laboratory manual. Variables for which no threshold is defined in the table below may be defined in the central laboratory manual.

Table 5 Thresholds for marked laboratory abnormalities

Laboratory test name (SI unit)	**LL**	**LLL**	**HH**	**HHH**
Hemoglobin (g/L)	< 100	< 80	Increase of > 20 g/L above ULN or above baseline (if baseline > ULN)	Increase of > 40 g/L above ULN or above baseline (if baseline > ULN)
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9/L)	< 75	< 50	> 600	> 999
Leukocytes (10^9/L)	< 3.0	< 2.0	> 20.0	> 100.0
Neutrophils (10^9/L)	< 1.5	< 1.0	NA	NA
Eosinophils (10^9/L)	NA	NA	> 5.0	NA
Lymphocytes (10^9/L)	< 0.8	< 0.5	> 4.0	> 20
ALT (U/L)	NA	NA	> 3 × ULN	> 5 × ULN
AST (U/L)	NA	NA	> 3 × ULN	> 5 × ULN
Alkaline phosphatase (U/L)	NA	NA	> 2.5 × ULN	> 5 × ULN
Total bilirubin (µmol/L)	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine (µmol/L)	NA	NA	> 1.5 × ULN	> 3 × ULN
Sodium (mmol/L)	NA	< 130	> 150	> 155
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable; SI = international system of units; ULN = upper limit of normal.