STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT 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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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
ADaM	Analysis data model
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
$AUC_{\tau, ss}$	Area under the plasma concentration-time curve during a dose interval at steady state
b.i,d.	Twice daily
BLQ	Below limit of quantification
CDISC	Clinical data interchange consortium
CI	Confidence interval
$C_{max, ss}$	Maximum plasma concentration at steady state
CSR	Clinical study report
$C_{trough, ss}$	Trough plasma concentration at steady state
CV	Coefficient of variation
CV_b	Inter-subject coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiograph
eCRF	Electronic case report form
EOS	End-of-study
EudraCT	European Union Drug Regulating Authorities Clinical Trials
IB	Investigator's Brochure
i.v.	Intravenous
ivSAF	intravenous Safety Analysis Set
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MSE	Mean squared error
PAH	Pulmonary arterial hypertension
PDs	Protocol deviations
PK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PR	Pulse rate

PT	Preferred Term
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RMP	Risk Management Plan
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS®	Statistical Analysis Software
SBP	Systolic blood pressure
SCR	Screened Analysis Set
SD	Standard deviation
SDTM	Study data tabulation model
SE	Standard error of the mean
SOC	System organ class
$t_{max, ss}$	Time to reach maximum plasma concentration at steady state
WHO	World Health Organization
WHO FC	WHO functional class
WHODD	WHO Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the derivation of safety and pharmacokinetic (PK) endpoints and the analyses and the presentation of analysis results and data for the clinical study report (CSR) of study AC-065A309.

Study data tabulation model (SDTM) datasets, including data from central labs and PK data provided by Actelion Data Management will be considered source data. Technical procedures and steps for processing these data and for implementing the definitions of variables for the purpose of the statistical analysis in analysis data model (ADaM) datasets will be covered in the analysis datasets specifications document.

In this SAP, 'Uptravi®' refers to the prescribed presentation of oral selexipag; whereas 'i.v. selexipag' refers to the intravenous (i.v.) presentation of selexipag, which is considered the study drug.

This SAP is based on the following study documents:

Table 1 Study documents

Document	Date, Version
Study Protocol	27JAN2017, Version 1 19APR2017, Version 1.DEU.A (local)
eCRF specifications	22SEP2017, Version 5
Protocol deviation code list	22FEB2017, Version 1.0
Selexipag (Uptravi®) EU Risk Management Plan	21JUN2017, Version 5.4
ECG data transfer specification	18AUG2017, Version 1.0
Definition of Marked Abnormalities in Laboratory Data (OTH-000005)	01NOV2017, Version 9

2 STUDY DESIGN AND FLOW

2.1 Study design

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

Approximately 20 subjects with stable pulmonary arterial hypertension (PAH), currently treated with Uptravi (oral selexipag) at a stable dose, i.e., unchanged dose for at least 28 days, will be enrolled in order to obtain 18 evaluable subjects. Subjects will be stratified based on their stable Uptravi dose:

- 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.

The study will be conducted at approximately 10 sites in 2 countries.

2.2 Study visit and assessment schedule

The study visit and assessment schedule is included in Appendix A.

2.3 Analysis periods

The study comprises five analysis periods:

Screening period: This period starts with the signing of the Informed Consent Form and ends with the first day of Period 1 (Visit 2 Day 1).

Period 1 (Uptravi, pre-treatment period, in-hospital): This period 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): This period starts in the morning of Visit 2 on Day 2 with the start of the first infusion of i.v. selexipag, and ends after approximately 36 hours in the evening of Visit 2 on Day 3 with the resuming of administration of Uptravi at the evening dose.

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

Safety follow-up period: This 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).

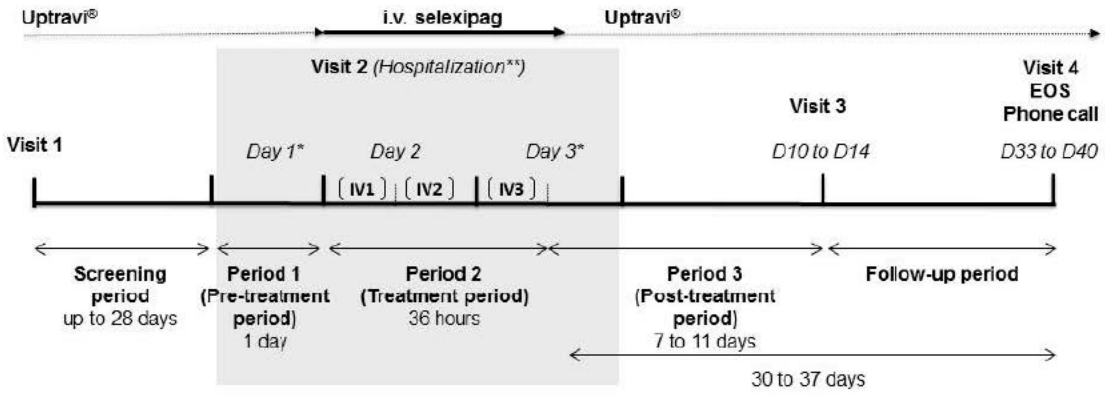
A summary of analysis periods is presented in Table 2:

Table 2 Summary of analysis periods

Period	Start	Stop
Screening period	Date/time of first Informed consent form signature	Prior to morning dose of Uptravi at Visit 2 Day 1
Period 1: Uptravi, pre-treatment period	Date/Time of Uptravi morning dose intake at Visit 2 Day 1	Prior to start of first infusion of i.v. selexipag at Visit 2 Day 2
Period 2: i.v. selexipag, treatment period	Start date/time of first infusion of i.v. selexipag at Visit 2 Day 2	Prior to evening dose of Uptravi at Visit 2 Day 3
Period 3: Uptravi, post-treatment period	Date/time of Uptravi evening dose intake at Visit 2 Day 3	Visit 3
Safety follow-up period	After end of Visit 3	End of Study

The study design and flow is shown in Figure 1 below. For details, refer to section 3 and section 7 of the AC-065A309 study protocol [D-17.055].

Figure 1 Study design and flow



* 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; PK = pharmacokinetic; V = visit.

2.4 Randomization and blinding

Not applicable, as this is a single-sequence, open-label study.

2.5 Sample Size

No confirmatory statistical tests are planned in the study.

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 adverse events (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 Analysis Set will ensure that, if the true rate of discontinuations due to prostacyclin-associated AEs is between 5% and 10%, the half-width of the 95% confidence interval (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 boundary of the CI for the i.v. Safety Analysis Set excludes values above 35%, and for the Safety Analysis Set, above 32%).

3 OBJECTIVES

3.1 Primary objective

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 (e.g., area under the plasma concentration-time curve during a dose interval at steady state [$AUC_{\tau, ss,}$], maximum plasma concentration at steady state [$C_{max, ss}$]) 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.

3.2 Other objectives

Other objectives of the study are:

- 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 a stable oral dose at steady state and after the switch from selexipag oral to selexipag i.v. in subjects with stable PAH.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

The following analysis sets were introduced in Section 10.1 of the protocol:

4.1.1 Screened Analysis Set

The **Screened Analysis Set** (SCR) includes all subjects who were screened and received a subject identification number.

4.1.2 Full Analysis Set

Not applicable in this study.

4.1.3 Safety Analysis Set

The Safety Analysis Set (SAF) includes all enrolled (included in the study on Day 1) subjects who received at least one dose of Uptravi or i.v. selexipag during any of Period 1, Period 2, or Period 3 of the study.

4.1.4 i.v. Safety Analysis Set

The i.v. Safety Analysis Set (ivSAF) includes all subjects who received at least one dose of i.v. selexipag.

4.1.5 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKS) comprises all subjects included in the SAF who received an Uptravi dose on Day 1 and the three doses of i.v. selexipag, and who complied with the protocol in a way that the PK measurements of the study are not affected. Protocol deviations resulting in an exclusion from the PKS are shown in Table 3.

Additional rules for exclusion from the PKS may be defined prior to database lock and reflected in this document.

Table 3 Protocol deviations leading to an exclusion from the PKS

Category	Protocol deviation code(s)	Identifier	Level of exclusion
Protocol deviation during screening period	206	Dose of Uptravi not stable for at least 28 days before Visit 2 (INCL 6)	Subject
	209	Subject with known and documented moderate and severe hepatic impairment (EXCL 2)	Subject
	210	Subject received gemfibrozil at any time since initiation of Uptravi (EXCL 3)	Subject
	214	Subject with renal failure and ongoing or planned dialysis (EXCL 7)	Subject
	217	Subject with another investigational treatment within 3 months of Visit 1 (EXCL 10)	Subject
Protocol deviation during treatment and observation period	305	Pre-dose PK blood sample collected after the morning dose on Day 1 or Day 3	Data point*
	306	Any post-AM dose PK sample collected after administration of the following PM dose on Day 1 or Day 3	Data point*
	316	Uptravi was not interrupted during i.v. selexipag treatment	Subject
	312	25 min or 87 min post-infusion start PK blood sample on Day 3 collected from the same arm as the infusion line	Data point*
	313	Subject did not discontinue i.v. selexipag treatment despite missing one infusion	Subject
	318	Dose of PAH medications (including diuretics) not stable between Visit 1 (screening) and last PK blood sample collection on Day 3	Subject
	321	Uptravi not administered or Uptravi dose missing on Day 1	Subject
	322	Uptravi dose on Day 1 is different from stable dose at Visit 1 (screening)	Subject
	323	Any i.v selexipag dose is not corresponding to subject's stable dose of Uptravi (i.e., $\geq$ 225 ug))	Subject

* If 2 or more data points are excluded from a 12-hour PK profile (i.e., on Day 1 or Day 3), the subjects must be excluded from the PKS. i.v. = intravenous; PK = pharmacokinetic; PKS = Pharmacokientic Analysis Set.

4.2 Usage of the analysis sets

An overview on the usage of the analysis sets for summary tables and listings is given in Table 4.

Table 4 Overview of the different analysis sets and their usage

Analyses/ Data Displays	Screened analysis set	Safety analysis set	i.v. Safety analysis set	Pharmacokinetic analysis set
Demographic data (ICH E3 14.1)				
Subject disposition	✓	(✓)*		
Protocol deviations	✓			
Inclusion/ Exclusion in Analysis Sets	✓			
Subject characteristics (Demographics, disease characteristics, medical history)		✓		
Concomitant therapy		✓		
Study completion		✓		
Study treatment exposure and compliance		✓	✓**	
PK data				
PK endpoints, Period 1 & 2				✓
Safety data (ICH E3 14.3)				
Adverse Events, Clinical Laboratory, ECG, Vital Signs, Body Weight and WHO FC**				
Period 1		✓		
Period 2			✓	
Period 3			✓	
Period 1 & 2		✓		
Period 2 & 3& FU			✓	
Period 1 & 2 & 3 & FU		✓	✓	
Appendices (ICH E3 16.1.7 and 16.2)				
All data collected in the clinical database				
Listings	✓	✓		

* Denominators for disposition will be based on the safety set. ** Tables will be produced for the SAF only if SAF and i.v. SAF are identical. ECG = electrocardiograph; FU = Safety Follow-Up; i.v. SAF = intravenous Safety Analysis Set; PK = pharmacokinetic; SAF = Safety Analysis Set; WHO FC = World Health Organization functional class.

5 STUDY SUBJECTS VARIABLES AND ANALYSES

All summaries described in this section will be displayed separately for the two subject cohorts, i.e., subjects treated with Uptravi 200–1000 µg b.i.d. and 1200–1600 µg b.i.d., as well as for all subjects in the analysis set.

The summary tables, figures and listings will use the analysis sets shown in Table 4.

5.1 Subject disposition

The summaries of subject disposition and screening failures will be prepared on the SCR. Summaries of study completion/discontinuation and study treatment completion/discontinuation will be prepared on the SAF:

5.1.1 Subject disposition and enrollment into analysis periods

Subject disposition will be summarized by presenting the number of subjects screened, enrolled and then number and percentage of subjects entering each analysis period [see Section 2.3], number and percentage of subjects treated with one, two, and three doses of i.v. selexipag as well as the number and percentage of subjects completing or discontinuing i.v. treatment or the study.

In addition, a summary of disposition by site and country will be prepared.

5.1.2 Screening failures

Screening failures are subjects who were not enrolled into the study, i.e., subjects who did not enter Period 1 of the study.

The number of screening failures will be shown in the disposition table. Reasons for screening failure will be listed.

5.1.3 Study completion/discontinuation

Subjects who received at least one dose of i.v. selexipag and who have completed the follow-up period will be considered study completers.

Subjects may discontinue from the study by withdrawal of consent, loss to follow-up, death, or investigator or sponsor decision. Details of study discontinuation are collected in the electronic case report form (eCRF).

The number and percentages of subjects who completed or prematurely discontinued the study, and reasons for discontinuation from the study will be summarized in a table and in a listing.

5.1.4 Study treatment completion/discontinuation

The number and percentage of subjects who completed or prematurely discontinued i.v. selexipag treatment, and reasons for premature discontinuation from i.v. selexipag treatment as captured in the eCRF will be summarized in a table and in a listing.

5.2 Protocol deviations

The analysis of protocol deviations (PDs) will be prepared on the SCR.

PDs will be based on the PD code list. The PD code list may be updated during the course of the study, but before database closure. The number and percentage of subjects who had an important PD will be summarized overall. All PDs will be summarized overall and by country.

All PDs will be listed. This listing includes all deviation descriptions, identifiers and categories.

5.3 Exclusion from analysis sets

The number and percentage of subjects in each analysis set, as described in Section 4.1, will be summarized in a table together with the number and percentage of subjects excluded from any analysis set, together with the reasons for exclusion. A listing of subject participation in the different analysis sets will be produced.

5.4 Subject characteristics

Subject characteristics will be summarized on the SAF.

5.4.1 Demographics

Baseline demographics, body weight and height will be summarized. The summary will include:

- Age (years)
- Sex (categorized as: Male, Female)
- Race (categorized as: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other)
- Ethnicity (categorized as: Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Body weight (kg)
- Height (cm)
- Country (assigned in the eCRF based on the list of sites).

In addition, the following variables will be derived:

- Age (years) in category, i.e., > = 18 – < 65, > = 65 years
- Body mass index (kg/m^2)

Demographic characteristics will be summarized using descriptive statistics for continuous and categorical data. Demographic characteristics will also be listed.

For disclosure of results to EudraCT, a summary table will be created showing age (years) in categories 18–64, 65–84, and > = 85.

5.4.2 Baseline disease characteristics

Baseline disease characteristics comprise the specific medical history (time since the initial diagnosis of PAH, and etiology of PAH as well as Uptravi dose) assessed at the screening visit and the WHO functional class (WHO FC) at Day 1.

Baseline disease characteristics will be summarized using descriptive statistics for continuous and categorical data. Time since initial diagnosis of PAH will be summarized in months.

Baseline disease characteristics will be listed.

5.4.3 Other baseline characteristics

The results of a physical examination will be listed.

5.4.4 Medical history

Medical history includes relevant previous and/or concomitant diseases or diagnoses prior to or ongoing at Screening visit, respectively. They are recorded on the 'Medical History' eCRF page. Reported terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at database lock, Version 21.0.

Previous diseases or diagnoses are medical history events which are not ongoing at screening, i.e., they have an end date prior to or equal to the Screening visit.

Concomitant diseases or diagnoses are all medical history events that are not considered as previous events.

Previous and concomitant diseases/diagnoses will be summarized separately by tabulating the number and percentages of subjects with each disease/diagnosis by system organ class (SOC) and preferred term (PT).

Previous and concomitant medical diseases/diagnoses will be listed.

5.4.5 Previous and concomitant therapies

Previous and concomitant therapies are collected continuously in the eCRF. The reported names will be coded using the WHO drug code dictionary (WHODD) and the anatomic therapeutic chemical (ATC) class code.

Previous therapies are therapies which ended prior to baseline [see Section 10.2].

Ongoing therapies are therapies that were started prior to baseline and are ongoing at study treatment start.

Study concomitant therapies are therapies that were started or dose changed (of those ongoing at baseline) during the respective analysis period [see Table 2].

Previous therapies, ongoing therapies, and study concomitant therapies will be summarized separately by Level 4 ATC class and PT. The study concomitant therapies summary will be displayed by study period.

The summaries will exclude PAH-specific therapies [see Section 5.4.5.1].

All recorded terms will be reported together in one listing together with flags indicating the type of therapy.

5.4.5.1 PAH-specific therapies

PAH-specific therapies will be identified by a search of WOHDD PTs and ingredients as shown in Table 5. Specific summaries will be prepared:

Ongoing PAH-specific therapies at baseline will be summarized. PAH-specific therapies that are newly started, dose changed, or stopped during any study period will be listed in a separate listing.

PAH-specific therapies will be displayed in a listing with the respective study period flagged.

Table 5 PAH-specific therapies

Category	Subcategory	Ingredient names
Antihypertensives for pulmonary arterial hypertension	ERAs	Ambrisentan, Bosentan, Macitentan
	PDE-5 inhibitors	Sildenafil, Tadalafil, Vardenafil
	sGC stimulator	Riociguat
Prostanoids		Epoprostenol, Treprostinil, Iloprost,
Uptravi		Selexipag

Categories are identified by searching the coded WHODRUG preferred terms for occurrence of any of the ingredient names, e.g., 'Sildenafil' and 'Sildenafil Citrate' will both be assigned to PDE-5 inhibitors.
ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; sGC = soluble guanylate cyclase.

5.4.5.2 Auxiliary medications

Oral Uptravi is collected as a mandatory background drug in the previous and concomitant medication page. Dose changes will be listed with PAH-specific therapies.

5.5 Study treatment exposure and compliance

i.v. selexipag is considered the only study treatment for this study.

5.5.1 Exposure

5.5.1.1 Exposure to i.v. selexipag

The number and percentage of subjects being exposed to one, two, or three infusions of i.v. selexipag will be summarized.

The planned i.v. selexipag dose [µg] for each infusion will be summarized as a continuous variable as well as a categorical variable using categories from Table 6. The actual i.v. selexipag dose will be summarized separately. Total actual time of infusion in minutes will be summarized for each of the three infusions as well.

The summary will be conducted for each of the three infusions separately.

The dosage administration records will be listed together with the reasons for dose change and dosage end as recorded in the eCRF.

5.5.1.2 Exposure to Uptravi prior and post- i.v. selexipag

The actual Uptravi dose [µg] will be collected and summarized by dose category for the four time points surrounding the i.v. administration of selexipag, i.e., evening dose before Visit 2 Day 1, morning and evening dose at Visit 2 Day 1 and evening dose at Visit 2 Day 3.

The Uptravi dosage records will be listed.

5.5.1.3 Shift in selexipag dose between oral and i.v. treatment

The shift from actual oral to i.v. and back to oral doses will be analyzed graphically in a series plot showing the individual dose in [µg] for each dose administration time point during Day 1 through Day 3 of Visit 2.

The i.v. selexipag doses administered will be converted to their oral dose equivalents [see Table 6] to facilitate the review.

5.5.1.4 Study treatment adjustments or interruptions, end of infusion status

Incidence of and reasons for i.v. administration interruption as well as the end of infusion status (irrespective of whether study treatment was completed as per protocol or not) will be summarized for each of three infusions.

5.5.2 Compliance with study treatment

Compliance with i.v. selexipag treatment is defined as the percentage of the actual dose infused compared with the planned dose to be infused, for each infusion and overall.

The planned dose to be infused will be determined from Table 6 below and based on the subjects' stable Uptravi dose taken from the Visit 2 Day 1 evening dose.

Table 6 Correspondence of i.v. selexipag dose compared 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

The actual infused dose will be computed by computing the product of the infusion rate (mL/h) with the concentration of infusion solution (µg/mL) as recorded in the eCRF and the elapsed time between start and end time (h) for each infusion to obtain the amount of i.v. selexipag infused.

Missed infusions will be entered with 0 µg actual infusion into the compliance analysis.

The planned dose, actual dose, and resulting compliance will be listed. Compliance will be summarized descriptively for each period and overall.

6 EFFICACY VARIABLES AND ANALYSES

Not applicable in this study.

7 SAFETY VARIABLES

7.1 Overview of safety analyses including subgroup analyses

7.1.1 Overview of safety and tolerability endpoints

Safety endpoints in this study comprise the incidence of AEs and serious AEs (SAEs), discontinuations due to AEs, change and newly occurring abnormalities in vital signs, ECG and clinical laboratory values, as well as change in WHO FC and body weight.

The analysis of safety endpoints in different analysis periods [see Table 2] is summarized in Table 7 below.

Table 7 Overview of safety and tolerability endpoints and populations in planned analysis periods

Endpoint	SCR (Scr)	1 (S)	2 (ivS)	3&FU (ivS)	1&2 (S)	2&3&FU (ivS)	1&2&3&FU (S, ivS)
Main safety and tolerability endpoints							
AEs and SAEs	✓	✓	✓	✓	✓	✓	✓
Prostacyclin-associated AEs [1] leading to discontinuation of study drug			✓				
Prostacyclin-associated AEs[1]		✓	✓	✓	✓	✓	✓
Injection site reaction AEs[1]			✓				
PAH related AEs[1]		✓	✓	✓	✓	✓	✓
Other safety and tolerability endpoints							
AEs leading to discontinuation of study drug			✓				
AEs related to study drug as judged by the investigator			✓	✓		✓	✓
Deaths during study							✓
ECG abnormalities, QT prolongation		✓	✓	✓	✓	✓	✓
Marked laboratory abnormalities		✓	✓	✓		✓	✓
Marked blood pressure abnormalities		✓	✓	✓		✓	✓
Change from baseline in WHO functional class [2]		✓	✓	✓	✓	✓	✓

Periods connected by an ampersand will be analyzed combined.
All analyses will be run on the S, if S and ivS are identical.
[1] As defined by MedDRA search terms [2] By visit analyses
(S) = Safety analysis Set, (ivS) = i.v. Safety analysis set, (Scr) = Screened subject set; AE = adverse event; ECG = electrocardiograph; FU = Safety Follow Up; MedDRA = Medical Dictionary for Regulatory Activities; PAH = pulmonary arterial hypertension; SAE = serious adverse event; SCR = Screening period, WHO = World Health Organization.

7.2 Adverse events

7.2.1 Variables

The original verbatim terms used by investigators to identify AEs in the eCRF will be mapped to PTs using the MedDRA dictionary using the latest version at data cutoff. The AE PTs will be then grouped by MedDRA PTs into frequency tables according to primary SOC.

7.2.1.1 Treatment-emergent adverse events

The analysis of AEs in Period 2, Period 3 and safety follow-up period is considered analysis of treatment-emergent events, as the i.v. formulation is the investigational treatment.

7.2.1.2 Adverse events related to study treatment

An AE will be considered related to the study treatment if the investigator answered 'yes' to the question 'Causal relationship to i.v. selexipag' or if it is missing.

7.2.1.3 Serious adverse events

An AE will be considered serious if the investigator answered 'Yes' to the question 'Serious?' or if information is missing.

7.2.1.4 Adverse events leading to discontinuation of study treatment

An AE is considered as leading to discontinuation of study treatment if the investigator ticked 'Drug withdrawn' on the question 'Action taken with study treatment'.

7.2.1.5 Injection site reactions

Injection site reactions will be collected on a separate eCRF page. Clinically significant injection site reactions will be reported as an AE.

7.2.1.6 Prostacyclin-associated AEs

Prostacyclin-associated AEs are AEs associated with the pharmacological action of selexipag that have been observed frequently, in particular during the phase of individualized dose titration. According to selexipag Investigator's Brochure (IB) reference safety information, these PTs include headache, diarrhea, nausea, vomiting, jaw pain, myalgia, pain in the extremity, flushing, and arthralgia.

7.2.1.7 AEs of special interest based on the Uptravi Risk Management Plan

For completeness, AEs will be analyzed according to the Uptravi Risk Management Plan (RMP) important identified or potential risks, using searches of MedDRA PTs provided by Global Drug Safety at the time of database closure. In accordance with the RMP, the following categories will be analyzed:

- Hypotension
- Anemia, decrease in hemoglobin concentration

- Hyperthyroidism
- Major adverse cardiovascular events
- Acute renal failure
- Bleeding events
- Light-dependent non-melanoma skin tumors
- Ophthalmological effects associated to retinal vascular system
- Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction).

7.2.1.8 PAH-related AEs

PAH-related AEs are AEs that are coded to the following MedDRA (Version 21.0) PTs:

Atrial fibrillation	Lung transplant
Atrial flutter	Pulmonary arterial hypertension
Atrial natriuretic peptide abnormal	Pulmonary arterial pressure abnormal
Atrial natriuretic peptide increased	Pulmonary arterial pressure increased
Acute right ventricular failure	Pulmonary oedema
Cardiac failure	Pulmonary hypertension
Cardiac index decreased	Pulmonary hypertensive crisis
Cardiogenic shock	Right atrial dilatation
Cardiopulmonary failure	Right atrial pressure increased
Chronic right ventricular failure	Right ventricular dysfunction
Cor pulmonale	Right ventricular failure
Cor pulmonale acute	Syncope
Oedema peripheral	Vascular resistance pulmonary increased
Jugular vein distension	

7.2.1.9 Non-serious AEs

For the disclosure of the results to EudraCT and ClinicalTrials.gov, non-serious AEs are defined. A non-serious AE is any AE with the question “Serious?” answered “No” by the investigator.

7.2.2 Analysis

The start date/time of the AE record from the CRF will be used to assign the AE to a study period.

Summary tables will be prepared as described in Table 8 for the periods mentioned in Table 7, except for the screening period.

Summary tables by SOC and PT will display the number and percentages of subjects with at least one AE in the respective primary SOC and at least one AE at the PT level. Summaries will be sorted by descending total frequency of SOCs and PTs and alphabetically in case of ties.

Summary tables by PT will display the number and percentages of subjects with at least one AE in the respective PT. Summaries will be sorted by descending total frequency of PTs and alphabetically in case of ties.

AEs occurring during the Screening period, i.e., prior to first dose of Uptravi on Visit 2 Day 1, will be listed.

Due to the small number of subjects, conservative 95% Clopper-Pearson CIs for the proportions will be computed using exact methods.

All AEs occurring during the study from date of informed consent signature to EOS will be listed.

For any injection site reaction (irrespective of clinical significance), the worst grade, criteria of the injection site reaction, as well as its clinical significance will be summarized. Any AEs associated with clinically significant injection site reactions will be summarized by PT and by maximum intensity in the AE table.

Table 8 Overview of adverse event analyses

Category	Approach
All AEs	- N (%) of subjects having at least one AE by primary SOC and PT - N (%) of subjects having at least one AE by PT - N (%) of subjects having at least one AE by PT and maximum intensity - Listing
SAEs	- N (%) of subjects having at least one SAE by PT - Listing
Injection site reaction AEs	- N(%), grade and diagnosis criteria of injection site reactions - N (%) of subjects having at least one clinically significant injection site reaction by PT and maximum intensity - Listing of PTs and specific details
Prostacyclin-associated AEs	- N (%) of subjects having at least one prostacyclin associated AE by PT - N % of subjects having at least one prostacyclin associated SAE by PT - N % of subjects having least one prostacyclin associated AE leading to discontinuation of study drug by PT - Listing
AEs of special interest based on the Uptravi RMP	- N (%) of subjects having at least one AE by RMP category and PT - N % subjects having at least one SAE by RMP category and PT (Listing) - N % least one AE by RMP category leading to discontinuation of study drug by RMP category and PT - Listing
PAH-related AEs	- N (%) of subjects having at least one event by PT - Listing of events
Any AE leading to discontinuation of study drug	- N (%) of subjects having at least one event by PT - Listing of events
AEs related to study drug as judged by the investigator	- N (%) of subjects having at least one event by PT - Listing of events

AE = adverse event; PAH = pulmonary arterial hypertension; PT = Preferred Term; RMP = Risk Management Plan; SAE = serious adverse event; SOC = System Organ Class.

7.2.2.1 Summaries of adverse events for public disclosure

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and not for the purpose of the clinical study report), treatment-emergent (S)AEs will be summarized displaying, for each dose group, counts and percentages of subjects with at least one treatment-emergent event plus the number of events (counted exactly the number of times they occurred also within a subject) by SOC and individual PT. The summary table is presented in descending order according to the overall incidence (i.e., SOC and

individual PT within each SOC with the highest number of occurrences appears first). Equal frequency of different individual PTs is sorted in alphabetical order of the individual PT.

The following summaries will be prepared according to the guidelines stated above:

- Summary of treatment-emergent SAEs
- Summary of treatment-emergent SAEs judged to be treatment related by the investigator
- Summary of treatment-emergent SAEs with fatal outcome
- Summary of treatment-emergent SAEs with fatal outcome judged to be treatment related by the investigator
- Summary of non-serious AEs with an incidence of 5% or higher in any treatment group

7.3 Deaths

Date of death and primary cause will be recorded on the 'Death' eCRF page. A listing including all deaths recorded in the database will be provided.

A separate listing will be provided displaying all AEs leading to death, i.e., with outcome 'fatal'.

7.4 Laboratory

A central laboratory will be used for all protocol-mandated tests. Laboratory values analyzed by local laboratories will only be listed.

Laboratory test results will be converted into Standard International units by the laboratory. Values outside the laboratory normal ranges will be flagged as well.

7.4.1 Measurements

Laboratory test results will be transferred from the central laboratory and provided in the SDTM structure, together with corresponding reference ranges in original, conventional, and standardized units. Assessments are performed at Screening visit, Visit 2 Day 1 (if more than 7 days after screening), Visit 2 Day 3, Visit 3, and at unscheduled visits based on the judgment of the investigator.

The following variables are collected as per protocol:

Hematology

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

For women of childbearing potential, urine pregnancy tests are performed at Screening Visit, Visit 2 Day 1, and Visit 4 (EOS). A pregnancy will be reported as an SAE; the results of the pregnancy tests will not be included in the clinical database.

7.4.2 Variables

For parameters assessed as a continuous variable, the following variables will be defined:

- Baseline
- Value at each post-baseline visit
- Absolute change from baseline to each post-baseline visit
- Position against reference ranges based on normal ranges provided by the laboratory.
- Position against marked abnormality range based on ranges provided in Appendix D.

7.4.3 Analysis

All laboratory values will be listed. Values from local laboratories will be flagged in data listings and not used in any analysis.

7.4.3.1 Values over time

For continuous laboratory variables, descriptive statistics will be provided for observed values as well as for change from baseline at each scheduled study visit.

7.4.3.2 Individual subject changes

Laboratory test results from both, scheduled and unscheduled visits will be used to determine the incidence of markedly abnormal test results. The date of the sample will determine the analysis period the test is assigned to.

The number of subjects with newly occurring or worsening markedly abnormal laboratory values will be displayed for the analysis sets shown in Table 4 and the periods shown in Table 7.

The definitions of marked abnormal lab values are shown in Appendix D.

7.5 Vital signs, physical findings, and other observations related to safety

7.5.1 Vital signs

Vital signs will be collected in an eCRF. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) and pulse rate (PR) assessed in supine position will be entered in mmHg. Height (cm) and weight (kg) will be assessed in subject wearing indoor clothing without shoes.

7.5.1.1 Measurements

Height (cm) will be assessed at Screening Visit.

Body weight will be assessed at Screening visit, Visit 2 Day 1, Visit 2 Day 3, Visit 3 and at unscheduled visits.

SBP, DBP, and PR will be assessed at Screening visit, Visit 2 Day 1, Visit 3 and at unscheduled visits. Further assessments will be conducted at pre-specified time points in Period 2, i.e., Visit 2 Day 1 and Visit 2 Day 3 as shown in Table 9.

Table 9 Schedule vital signs monitoring in Period 2

Visit Day	Time point	Assessment Description
Visit 2 Day 2	0 h	Shortly before morning (AM) i.v. selexipag infusion
	25 min	During AM i.v. selexipag infusion, 25 min after infusion start
	87 min	Shortly before end of AM i.v. selexipag infusion
	4 h	Four hours after initiation of AM selexipag infusion
	6 h	Six hours after initiation of AM selexipag infusion
	8 h	Eight hours after initiation of AM selexipag infusion
	12 h	Before PM selexipag infusion, twelve hours after initiation of AM selexipag infusion
Visit 2 Day 3	0 h	Shortly before morning (AM) selexipag infusion
	25 min	During AM selexipag infusion, 25 min after infusion start
	87 min	Shortly before end of AM selexipag infusion
	4 h	Four hours after initiation of AM selexipag infusion
	6 h	Six hours after initiation of AM selexipag infusion
	8 h	Eight hours after initiation of AM selexipag infusion before oral administration of selexipag
	12 h	Before PM Uptravi intake, twelve hours after initiation of AM selexipag infusion

7.5.1.2 Variables

For vital signs parameters, the following variables will be defined:

- Baseline
- Value at each post-baseline visit
- Absolute change from baseline to each post-baseline visit
- Absolute change from pre-dose to each post-dose assessment.

For supine SBP (mmHg) and supine DBP (mmHg), the presence of post-baseline abnormalities is derived according to the criteria defined in Table 10 below:

Table 10 Marked abnormalities in blood pressure

Analysis Parameter	LL	L	Normal	H	HH
Supine SBP (mmHg)	-	SBP < 90	90 ≤ SBP < 140	140 ≤ SBP ≤ 159	SBP ≥ 160
	-	Decrease > 40 from baseline	-	Increase > 20 from baseline	-
Supine DBP (mmHg)	-	DBP < 50	50 ≤ DBP < 90	90 ≤ DBP ≤ 99	DBP ≥ 100
	-	Decrease > 20 from baseline	-	Increase > 20 from baseline	-

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Abnormalities will be flagged for each post-baseline assessment individually and overall for the study treatment period.

7.5.1.3 Analysis

Values over time

A listing of all vital sign parameters will be created displaying all values in the database regardless if from scheduled or unscheduled visits. Marked abnormal values will be flagged.

Descriptive statistics will be provided for observed values as well as for change from baseline to all visits.

Another descriptive summary will be provided for the absolute change from pre-dose to post-dose values for the visits where pre- and post-dose values are assessed.

Individual subject changes

The number and percentage of subjects with at least one marked newly occurring or worsening abnormality for blood pressure will be summarized by period (Period 2, Period 3/ Safety follow-up [FU]) and overall (Period 2, 3, and FU combined) as shown in Table 7.

7.5.2 Physical findings

Physical examination will be conducted at screening, may be repeated at Visit 2 Day 1, and will be conducted at Visit 3.

The results of the physical examination will be listed. New abnormal physical findings will be reported as AEs.

7.5.3 WHO functional class

WHO FC (Class I–IV) as assessed by the investigator will be collected in the eCRF.

7.5.3.1 Measurements

WHO FC will be assessed at Screening Visit, Visit 2 Day 1, Visit 2 Day 3 (after the end of the last infusion), Visit 3, and at unscheduled visits.

7.5.3.2 Variables

For WHO FC, the following variables will be defined:

- Baseline value
- Value at each post-baseline visit
- Shift from baseline to each post-baseline visit
- Worst (highest) post-baseline value
- Best (lowest) post-baseline value.

7.5.3.3 Analysis

Values over time

A listing of all WHO FC assessments will be created displaying all values in the database, regardless if from scheduled or unscheduled visits.

Descriptive statistics (frequency tables) will be provided for observed values as well as for shift from baseline to all visits.

Individual subject changes

The worst/best post-baseline WHO FC will be displayed along with a shift table from baseline to worst/best post-baseline value.

7.6 Electrocardiograph

A standard 12-lead electrocardiograph (ECG) will be conducted on subjects in fully rested supine position. All ECG data from scheduled and unscheduled visits will be transferred to a central ECG laboratory. The ECG readouts (see below) will be transferred from the central ECG laboratory to trial data management and imported in the trial database.

7.6.1 Variables

The 12-lead ECG encompasses 3 categories of data obtained via the central ECG laboratory:

- Measurements:
  - ECG mean heart rate
  - PR interval,
  - QRS duration,
  - QT interval,
  - QTcB interval,
  - QTcF interval,
- Interpretation (normal/abnormal/unable to evaluate)
- Qualitative findings by category, as specified in the ECG data transfer specifications:

Table 11 Pre-specified ECG findings categories

Category
Atrioventricular Conduction
Axis and Voltage
Chamber Hypertrophy or Enlargement
Intraventricular-Intraatrial Conduction
Myocardial Infarction
Pacemaker
Sinus Node Rhythms and Arrhythmias
Supraventricular Arrhythmias
Supraventricular Tachyarrhythmias
ST Segment, T Wave and U wave
Ventricular Arrhythmias
Ventricular Tachyarrhythmias

ECG assessments will be performed at Visit 2 Day 1, Visit 2 Day 2 (pre-dose and 30 min after end of infusion for each of the two infusions), Visit 2 Day 3 (pre-dose and 30 min after end of infusion), Visit 3, and at unscheduled visits.

7.6.2 Variables

The following variables will be defined for the analysis of ECG parameters:

- Baseline values of quantitative ECG parameters
- Value at each post-baseline visit
- Absolute change from baseline to each post-baseline visit
- Absolute change from pre-dose after each infusion
- Proportion of qualitative ECG abnormalities

In addition, the incidence of QT prolongations is derived according to the criteria defined in Table 12 below:

Table 12 QT prolongations in ECG parameters

Analysis Parameter	Analysis Variable(s)	Analysis Criterion
QTcB (msec) QTcF (msec)	Analysis value	- Value > 450 - Value > 480 - Value > 500
	Change from baseline	- Increase from baseline > 30 - Increase from baseline > 60
	Analysis value and change from baseline	- Value > 450 and increase from baseline > 30 - Value > 450 and increase from baseline > 60

ECG = electrocardiograph; QTcB = QT interval corrected using Bazett's formula;
QTcF = QT interval corrected using Fridericia's formula.

7.6.3 Analysis

7.6.3.1 Values over time

A listing of all ECG measurements will be created displaying all values in the database. Abnormal ECG values will be flagged.

The overall interpretation and the findings will be presented in a separate listing.

For each parameter at each time over the course of the study, quantitative descriptive statistics for the value at the visit and the change from baseline will be presented by parameter and by time point.

Another descriptive summary will be provided for the absolute change from pre-dose to post-dose values in quantitative ECG parameters for the visits where pre- and post-dose values are assessed.

7.6.3.2 Individual subject changes

The number and percentage of subjects with at least one newly occurring or worsening abnormality for ECG parameters as defined in Table 12 is provided by period as shown in Table 7.

In addition, qualitative ECG findings will be tabulated by overall interpretation (normal, abnormal/unable to evaluate), and category [see Table 11].

7.7 Subgroup analysis of safety variables

In general, all safety variable summaries are presented by dose cohort as for study subject analyses [see Section 5].

No *a-priori* subgroup analyses are planned at this point.

7.8 Pharmacokinetic variables

7.8.1 Measurements

PK blood samples are collected at Visit 2 Day 1 (seven samples) and Visit 2 Day 3 (seven samples) to obtain 12-hour PK profiles of selexipag and its active metabolite, ACT-333679, at steady state for Uptravi and i.v. selexipag, respectively.

Endpoints derived during Period 1 are thus connected to Uptravi (Day 1) and endpoints during Period 2 are connected to i.v. selexipag (Day 3).

7.8.2 Pharmacokinetic endpoints

The following PK endpoints will be determined:

- $AUC_{\tau, ss}$ of selexipag and its active metabolite, ACT-333679, after Uptravi (oral selexipag) in Period 1 and after i.v. selexipag administration in Period 2.
- $C_{max, ss}$ 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.

7.8.3 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 limit of quantification (LOQ) during one dosing interval at steady state.

7.8.3.1 Dose normalization

Dose normalization will be conducted to the lowest prescribed selexipag dose (200 µg for oral Uptravi and 225 µg for i.v. selexipag).

Dose normalized plasma concentrations, $C_{trough,\ ss,\ norm}$,$C_{max,\ ss,\ norm}$ and $AUC_{\tau,\ ss,\ norm}$ will be determined by dividing the respective parameters by the actual dose and multiplying with 200 or 225 for Uptravi and i.v. selexipag parameters, respectively.

7.8.4 Analysis

All PK parameters will be listed for all subjects providing PK data. All analyses will be conducted on the PKS.

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.

7.8.4.1 Plasma concentrations

The PK expert will examine the plasma concentration data and identify implausible values.

Plasma concentrations of selexipag and ACT-333679 will be listed per subject, time point, and period (i.e., for Uptravi and i.v. selexipag). Implausible plasma concentrations of selexipag or ACT-333679 will be flagged in the listings.

Plasma concentrations of selexipag and ACT-333679 will be summarized per time point by dose, including dose normalized, and period (i.e., for Uptravi and i.v. selexipag). Implausible plasma concentrations of selexipag or ACT-333679 will not be included in the summary statistics.

Implausible values will be indicated in the comments value variable (COVAL) of the comments dataset (CO). The reference link (COREF) will be used to join these implausible values with time points of the plasma concentration dataset (PC).

7.8.4.2 Trough concentrations

Selexipag and ACT-333679 $C_{trough,\ ss}$ will be listed by dose, subject, and period as well as the ratio of the periods per subject.

Summary statistics will be provided by dose, including dose normalized, and by period. Implausible $C_{trough,\ ss}$ values will be flagged in the listings and not included in summary statistics.

7.8.4.3 $C_{max,\ ss}$, $t_{max,\ ss}$, and $AUC_{\tau,\ ss}$

$C_{max,\ ss}$, $t_{max,\ ss}$, and $AUC_{\tau,\ ss}$ of selexipag and ACT-333679 will be listed by dose, subject, and period. The ratio of the parameters between i.v. selexipag (test treatment) and Uptravi (reference treatment) per subject will be shown, except for $t_{max,\ ss}$. Any values

obtained from implausible plasma concentrations of selexipag or ACT-333679 will be flagged in the listings and not included in the statistical analysis.

Summary statistics will be provided by dose and period for selexipag and ACT-333679.

Dose-normalized $C_{max, ss}$ and $AUC_{\tau, ss}$ will be listed and summarized by period as well for selexipag and ACT-333679.

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

The ratio of $C_{max, ss}$ and $AUC_{\tau, ss}$ of selexipag and ACT-333679 between Uptravi and i.v. selexipag, after dose normalization, within each dose level (if sufficient subjects are enrolled per level) will be estimated by fitting a mixed effect model to the data using period (i.e., treatment) as fixed, and subject as random effect to the log-transformed $C_{max, ss}$ and $AUC_{\tau, ss}$ values. The ratios of geometric means between i.v. selexipag (test treatment) and Uptravi (reference treatment) will be computed and displayed together with their 90% CI by back-transforming the period contrasts and interval boundaries of the log-transformed data. If dose-proportionality is shown within each dose, then an overall model may be considered for robustness.

The inter-subject coefficient of variation (CV_b) of $C_{max, ss}$ and $AUC_{\tau, ss}$ of selexipag and ACT-333679 will be computed by using the mean squared error (MSE) of the mixed model as an estimate of variation.

Based on the previous studies QGUY/2006/NS304/-01, AC-065-101 and AC-065A201 it is known that the PK profile of selexipag and its active metabolite ACT-333679 is dose-proportional up to a single dose of 800 ug and for multiple doses of up to 1800 ug b.i.d. after oral administration.

Dose proportionality of $AUC_{\tau, ss}$ of selexipag and ACT-333679 after i.v. selexipag will be analyzed using the power model approach [Gough 1995], if at least three different dose levels with a sufficient number of subjects to compute CIs are included in the PKS. A plot of log dose versus log $AUC_{\tau, ss}$ including the slope of the estimated parameter will be displayed.

Differences in $t_{max, ss}$ of ACT-333679 between the i.v. selexipag period and the Uptravi period will be assessed within each dose level using a Wilcoxon signed rank test and displaying the median estimate and exact 90% CI of the location shift using Hodges-Lehmann estimation.

If considered appropriate, a sensitivity analysis may be conducted to evaluate the statistical impact of the plasma concentrations of selexipag or ACT-333679 that were considered implausible by the PK expert.

8 GENERAL STATISTICAL METHODOLOGY

All analyses described in this document will be performed by the contract research organization Datamap GmbH, Freiburg, Germany using Statistical Analysis Software (SAS®) version 9.3 or higher.

8.1 General rules for data presentations

This section describes the general rules applied for all data displays, unless otherwise specified in each corresponding section.

Data listings will show all assessments included in the study database, regardless if used in specific summary tables.

8.1.1 Summary statistics of non-PK data

Clinical data will be listed and summarized using appropriate descriptive statistics:

- For continuous variables: Number of non-missing observations, mean, standard deviation, minimum, median, and maximum.
- For dichotomous or categorical variables: Number of non-missing observations, and frequency with percentage per category. Denominators for percentages are the number of subjects in the pertinent analysis set and period, unless otherwise specified.

8.1.2 Summary statistics of PK data

PK data will be listed as described in Section 7.8.4 and summarized using appropriate descriptive statistics:

- Plasma concentrations of selexipag and ACT-333679 will be summarized using number of non-missing observations, arithmetic mean, geometric mean, standard deviation (SD), standard error of the mean (SE), minimum, median, maximum and 95% CIs for the arithmetic and geometric mean.
- $C_{trough,\ ss}$ of selexipag and ACT-333679 will be summarized using number of non-missing observations, arithmetic mean, geometric mean, SD, SE, coefficient of variation of the observed and logarithmized data (CV, CV_{ln}) in %, minimum, median, maximum and 95% CIs for the arithmetic and geometric mean.
- $C_{max,\ ss}$ and $AUC_{\tau,\ ss}$ of selexipag and ACT-333679 will be summarized using number of non-missing observations, arithmetic mean, geometric mean, SD, SE, CV%, CV_{ln}%, minimum, median, maximum, 95% CIs for the arithmetic and geometric mean.
- $t_{max,\ ss}$ of selexipag and ACT-333679 will be summarized using number of non-missing observations, arithmetic mean, SD, SE, CV%, minimum, median, maximum and 95% CI for the arithmetic mean.

8.2 Statistical methods

This section describes in general terms the statistical models and methods applied.

No confirmatory hypothesis testing will be conducted in this study. All tests and CIs will be of descriptive nature. Confidence levels are chosen as 90% for PK geometric means and 95% for all other confidence levels and will not be adapted for multiplicity.

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

8.2.1 Statistical methods for discrete data

8.2.1.1 Exact Pearson-Clopper CIs for the incidence of AEs

Due to the small number of subjects included in the trial, broader estimates for the incidence rates of AEs need to be computed. The Pearson-Clopper method yields exact, while conservative confidence limits, i.e., the CI is at least 95%. They will be computed using PROC FREQ as shown below, assuming the input dataset contains counts for each *aedecod,* with 0 indicating subjects without event and 1 indicating subjects with event.

```
PROC FREQ data=<input_dataset>;
BY aedecod;
TABLES event /exact binomial (level='1');
WEIGHT count;
RUN;
```

8.2.2 Statistical methods for continuous data

8.2.2.1 Differences between periods in $C_{max, ss}$ and $AUC_{\tau, ss}$ of selexipag/ACT-333679

Within each dose level and after dose normalization, differences between the Uptravi and i.v. selexipag periods will be analyzed by computing the geometric mean ratios of the respective period with the oral formulation as reference treatment in the denominator. This is done by fitting a mixed linear model to the log-transformed $C_{max, ss}$ and $AUC_{\tau, ss}$ values with period as fixed and subject as random effect. The Kenward-Rodgers method for calculation of degrees of freedom will be used to obtain degrees of freedom to calculate CIs. An unstructured covariance matrix will be assumed. The difference of the least squares mean and its 90% CI will be computed and transformed back to normal scale to obtain the geometric mean ratio. SAS® code similar to the code shown below will be used:

```
PROC MIXED data=<input_dataset>;
CLASS period;
MODEL log_response=period / DDFM=KR;
RANDOM intercept /subject=usubjid TYPE=UN;
ESTIMATE 'Difference i.v. - oral' period -1 1 /CL ALPHA=0.1;
RUN;
```

8.2.2.2 CV_b in $C_{max,\,ss}$ and $AUC_{\tau,\,ss}$ of selexipag/ACT-333679

The CV_b expressed in percent will be computed using the formula

$$CV_b\ [\%] = 100\sqrt{e^{S_b{}^2} - 1}$$

where S_b^2 is the MSE of the residuals from the mixed effects model described in Section 8.2.2.1.

8.2.2.3 Dose proportionality of $AUC_{\tau,\,ss}$ of selexipag/ACT-333679

To assess dose proportionality of selexipag the power model approach will be used:

The power model approach specifies a relationship between the scheduled dose D of i.v. selexipag and $AUC_{\tau,\,ss}$ of selexipag / ACT-333679 which is expressed as

$Y_{ij} = \alpha_j' * D_i^{\beta} * \varepsilon'_{ij}$

Together with α' denoting $\exp(\alpha)$ and ε'_{ij} denoting $\exp(\varepsilon'_{ij})$, logarithmizing both sides of the equation yields a linear model

$\log(Y_{ij}) = \alpha_j + \beta \log(D_i) + \varepsilon_{ij}$

with

Y_{ij} $AUC_{\tau, ss}$ of dose level i in subject j (i=1, …, I), (j=1, …, n)

α_j intercept parameter (assumed to be a random effect)

β the slope parameter

D_i size of dose level i

ε_{ij} random error term of subject j in dose level i.

This model equation can be fitted using a mixed linear model with $\log(D_i)$ as a covariate and subject as random effect. The 90% CI for the parameter estimate for the covariate will be computed. In case of dose proportionality, 1 should be included in the 90% CI of the parameter estimate.

SAS® code similar to the following will be used:

```
PROC MIXED data=<input_dataset>;
MODEL log_response=log_dose / DDFM=KR S CL ALPHA=0.1;
RANDOM intercept /subject=usubjid TYPE=UN;
RUN;
```

The assessment of dose proportionality using the power approach will only be conducted when at least three dose levels are included into the study.

8.2.2.4 Difference of $t_{max, ss}$ of ACT-333679

Within each dose level, difference in $t_{max, ss}$ of ACT-333679 between Periods 1 and 2 will be assessed by computing the Hodges-Lehmann estimator for shift in the median from Uptravi to i.v. selexipag. The median is computed by computing all shifts between the two periods and using the median of the shifts as an estimate. If computationally feasible, exact estimates and 90% CIs will be computed.

9 INTERIM ANALYSIS

No interim analysis is planned in this trial.

10 GENERAL DEFINITIONS AND DERIVATIONS

This section describes all recurrent general definitions (e.g., study treatment start date, baseline, study day) which will be used for the derivations of variables and summary tables and are not covered in the sections above.

10.1 Handling of screening and re-screening data

Data of re-screened subjects obtained at the re-screening visit will be used as 'Screening' data. If a data point is not collected at re-screening but was collected at the previous screening visit, the data point from the screening visit will be used.

10.2 Analysis periods and visit windows

10.2.1 Study treatment start and end date

The date and time of the first infusion of i.v. selexipag will be considered study treatment start date/time. The end date and time of the last infusion of i.v. selexipag will be considered study treatment end date/time.

10.2.2 Study days

The day of intake of the Uptravi during pre-treatment period, i.e., Period 1 [see Section 2.3] will be considered Day 1. There is no Day 0; the day before Day 1 will be considered Day –1.

Note that study treatment will be administered on Day 2 and Day 3 according to this definition; thus study day definition corresponds to the study days used in the study protocol.

10.2.3 Baseline

All assessments on Day 1 will be considered baseline. If a Day 1 assessment is not available, the last assessment prior to Day 1 will be considered baseline.

10.2.4 Unscheduled visits and visit windows

Assessments made on both, scheduled and unscheduled visits will be assigned to an analysis period according to Table 2 using the assessment date and time.

Furthermore, each assessment will be assigned an analysis visit using the time windows described in Table 13. If more than one assessment was made within a visit time window, the closest value to the target Visit is displayed in by visit displays.

Table 13 Analysis visit windows

Analysis visit	Nominal study day*	Lower bound study day*	Upper bound study day*
Visit 2, Day 1	Day 1	Day of informed consent	Day 1
Visit 2, Day 2	Day 2	Day 2	Day 2
Visit 2, Day 3	Day 3	Day 3	Day 3
Visit 3	Day 12	Day 4	Day 22
Visit 4	Day 33	Day 23	End of Study

* Study days are defined as in Section 10.2.2.

10.3 Uptravi dosage subgroups

Enrollment is controlled by an interactive response technology system based on the subject's stable Uptravi dose. For analysis purposes, the information entered into the system will determine the allocation to one of the two dosage subgroups.

10.4 Derived and computed variables for analysis datasets

CDISC ADaM version 2.1 and ADaM implementation guide 1.1 will be followed.

For details on the derivation of specific analysis variables, please refer to the programming specifications document.

10.5 Handling of missing/incomplete date and time fields

Missing parts for specific dates/times will be changed into acceptable non-missing values as described in the table below.

Type of date/time	Imputation method when date/time is incomplete	Imputation method when date/time is missing
Start Date/Time of Adverse Event	If the end date of the AE is not before the start of study treatment, and if the study treatment start falls in the range of possible dates, the study treatment start date is used. In all the other cases, the lower limit (i.e., first day of the month, 00:00h) is used.	Date & time of first i.v. selexipag
End Date/Time of Adverse Event	Use the upper limit of the range of possible dates given the nonmissing date/time parts, i.e., last day of the month or last day of the year, 23:59h	No approximation, the AE is considered ongoing at end of study

Start Date of Medication	If the date of the Screening visit is within the range of possible dates, use the Screening visit date. Otherwise, use first day of the month and/or first day of the year.	Date of Screening visit
End Date of Medication	Use the upper limit of the range of possible dates given the nonmissing date/time parts, i.e., last day of the month or last day of the year	No approximation, the medication is considered ongoing at the end of study
Date of initial diagnosis of PAH	Day missing: 15th of the month Day and month missing: 30th of June If the resulting date is later than the date of screening visit date and the lower limit is not later than the screening visit date, then the date is substituted with the date of screening visit.	No replacement
PK sample Date/Time	If the scheduled time is within the possible range given the nonmissing date/time parts, use the scheduled date/time. Otherwise, the sample date/time cannot be imputed.	No replacement

10.6 Handling of missing infusion durations

If the start time or end time of the infusion or the time point of the infusion rate increase is missing, study treatment administration times as stipulated in the protocol will be assumed for analysis, i.e., 15 min duration of the initial infusion rate and 72 min of the increased infusion rate.

11 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

This section describes changes to the statistical analysis planned in the protocol, and other deviations from the protocol relevant to the analysis or interpretation of the results.

11.1 Changes to the analyses planned in the study protocol

None.

11.2 Changes in the conduct of the study / data collection

None.

11.3 Clarifications concerning endpoint definitions and related variables or statistical methods

11.3.1 Treatment/period as factor in mixed model analysis

Protocol section 10.3.5 [D-17.055] states that the mixed model analysis of $C_{max,\ ss}$ and $AUC_{\tau,\ ss}$ contains terms for period, treatment and subject. Since 'period' and 'treatment' are confounded (Period 1: Uptravi, Period 2: i.v. Selexipag) only 'period' is used in the models.

11.3.2 Additional analyses as compared to the study protocol

- C_{trough} ratio of treatments per subject.
- Marked blood pressure abnormalities.

12 LIST OF TABLES, LISTINGS AND FIGURES

Since all tables, figures, and listings will be produced using SAS®, the outputs actually generated may slightly differ from the mock-ups presented in the study-specific mock-up catalogue.

12.1 Subject disposition

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DISP	T	Subject disposition	SCR	Y	T_DISP
DISP_COU	T	Subject disposition by country and site	SCR		T DISP CO U
ANA	T	Overview of analysis sets and reasons for exclusion from analysis sets	SCR		T_ANA
PWDS	T	Reasons for premature discontinuation from the study	SAF		T_PWDS

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.2 Protocol deviations

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PD	T	Summary of important protocol deviations	SCR		T_PD
PD_COU	T	Summary of all protocol deviations overall and by country	SCR		T_PD

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.3 Subject characteristics

12.3.1 Demographics and baseline disease characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
DEM	T	Summary of baseline demographic characteristics	SAF	Y	T_DEM
AGECATEU	T	EudraCT age categories	SAF		T_AGECATEU
BAS	T	Summary of baseline disease characteristics	SAF	Y	T_BAS

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.3.2 Other baseline characteristics

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PHYS	L	Listing of physical examination results	SCR		L_PHYS

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.3.3 Medical history

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
MH_PRV_SOC	T	Summary of previous diseases or diagnoses, by primary system organ class and preferred term	SAF		T_MH_SOC
MH_ONG_SOC	T	Summary of concomitant diseases or diagnoses, by primary system organ class and preferred term	SAF		T_MH_SOC

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.3.4 Previous and concomitant medications

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
CM_PRV	T	Summary of previous therapies by Anatomical Therapeutic Chemistry (ATC) Class and Preferred Term [Add footnote: *Previous therapies are therapies which ended prior to baseline.*]	SAF		T_CM
CM_ONG	T	Summary of ongoing therapies by Anatomical Therapeutic Chemistry (ATC) Class and Preferred Term [Add footnote: *Ongoing therapies are therapies which were started prior to baseline and are ongoing at study treatment start.*]	SAF		T_CM
CM_CM	T	Summary of study concomitant therapies by Anatomical Therapeutic Chemistry (ATC) Class and Preferred Term [Add footnote: *Study concomitant therapies are therapies which were started or dose changed (of those ongoing at baseline) during the respective period.*]	SAF		T_CM
CM_ONG_PAH	T	Summary of ongoing PAH specific therapies at baseline [Add footnote: *Ongoing therapies at study treatment start are therapies which were started prior to baseline and are ongoing at study treatment start.*]	SAF	Y	T_CMPAH

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.4 Study treatment exposure

12.4.1 Exposure

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
EXP_IV	T	Exposure to i.v. selexipag	ivSAF	Y	T_EXP_IV
EXP_PO	T	Exposure to Uptravi prior to and after i.v. selexipag	SAF ivSAF#		T_EXP_PO
COMPL_IV	T	Compliance to study treatment	ivSAF		T_COMPL_IV
EXP_ADJ	T	Summary of study treatment administration, reasons for interruptions and end of infusion	ivSAF		T_EXP_ADJ
EXP_SHF	F	Shift in selexipag dose between oral and i.v. treatment	ivSAF		F_EXP

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.4.2 Study treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PWDT	T	Reasons for premature discontinuation of i.v. selexipag treatment	ivSAF		T_PWDT

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.5 Study withdrawal

See Section 12.4.

12.6 Primary efficacy analyses

Not applicable.

12.7 Safety analyses

12.7.1 Adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_ALL_SOC	T	Incidence of adverse events by period, primary system organ class and preferred term	SAF ivSAF#	Y	T_AE_SOC
AE_INT	T	Incidence of adverse events by preferred term and maximum intensity	SAF ivSAF#		T_AE_PT_INT

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.2 Deaths and serious adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SAE_ALL_PT	T	Incidence of serious adverse events by period, and preferred term	SAF ivSAF#	Y	T_AE_PT
DTH	L	Listing of all deaths	SAF		L_DTH

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.3 Prostacyclin-associated adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_PC_PT	T	Incidence of prostacyclin-associated adverse events by period and preferred term	SAF ivSAF#	Y	T_AE_PT
SAE_PC_PT	T	Incidence of prostacyclin-associated serious adverse events by period and preferred term	SAF ivSAF#		T_AE_PT
AE_PCDC_PT	T	Incidence of prostacyclin-associated adverse events leading to discontinuation of study treatment by preferred term	SAF ivSAF#		T_AE_PT

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.4 Adverse events of special interest based on the Uptravi risk management plan

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_RMP	T	Incidence of adverse events of special interest based on the Uptravi risk management plan by period, risk category and preferred term [*Replace SOC with Risk category in the Shell Delete SOC on footnote regarding MedDRA version..*]	SAF ivSAF#		T_AE_SOC
SAE_RMP	L	Listing of all serious adverse events of special interest based on the Uptravi risk management plan [*Replace SOC with Risk category in the Shell.*]	SAF ivSAF#		L_AE
AE_DC_RMP	T	Incidence of adverse events of special interest based on the Uptravi risk management plan leading to discontinuation of study treatment by period, risk category and preferred term [*Replace SOC with Risk category in the Shell. Delete SOC on footnote regarding MedDRA version.*]	SAF ivSAF#		T_AE_SOC

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.5 Injection site reaction adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_INJ_INT	T	Incidence of clinically significant injection site reaction adverse events by preferred term and maximum intensity	ivSAF	Y	T_AE_PT_INT
AE_INJDET	T	Grade and diagnosis criteria of injection site reactions	ivSAF		T_AEINJ

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set.

12.7.6 PAH-related adverse events

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_PAH_PT	T	Incidence of PAH related adverse events by period and by preferred term	SAF ivSAF#		T_AE_PT

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.7 Adverse events leading to study treatment discontinuation

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_DC_PT	T	Adverse events leading to discontinuation of study treatment by preferred term	ivSAF		T_AE_PT

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set.

12.7.8 Adverse events related to study drug

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_REL_PT	T	Incidence of adverse events related to study treatment as judged by the investigator by period and by preferred term	ivSAF		T_AE_PT

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set.

12.7.9 Summaries of adverse events for disclosure

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SAE_CTGOV	T	Summary of treatment emergent SAEs	SAF		T_AE_SOC2
SAE_REL_CTGOV	T	Summary of treatment emergent SAEs judged to be treatment related by the investigator	SAF		T_AE_SOC2
SAE_DTH_CTGOV	T	Summary of treatment emergent SAEs with fatal outcome	SAF		T_AE_SOC2
SAE_DTHREL_CTGOV	T	Summary of treatment emergent SAEs with fatal outcome judged to be treatment related by the investigator	SAF		T_AE_SOC2
NSAE_5PCT_CTGOV	T	Summary of non-serious AEs with an incidence of 5% or higher in any treatment group	SAF		T_AE_SOC2

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.7.10Laboratory tests

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
LB_SUM_HEM	T	Summary and change from baseline of hematology values, by visit	SAF ivSAF#		T_LB_SUM
LB_SUM_CHE	T	Summary and change from baseline of biochemistry values, by visit	SAF ivSAF#		T_LB_SUM
LB_ABN_P2	T	Incidence of marked laboratory values, by period	SAF ivSAF#		T_LB_ABN

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.11Vital signs and body weight

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
VS_WGT_SUM	T	Summary and change from baseline of body weight, by visit	SAF ivSAF#		T_LB_SUM
VS_SUM	T	Summary and change from baseline of vital signs, by visit	SAF ivSAF#		T_VS_SUM
VS_PREDS	T	Summary of post-dose values and change from pre-dose of vital signs, by visit	SAF ivSAF#	Y	T_VS_PREDS
VS_ABN	T	Incidence of marked blood pressure abnormalities, by period	SAF ivSAF#	Y	T_VS_ABN

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.12ECG

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
EG_SUM	T	Summary and change from baseline of quantitative ECG parameters, by visit	SAF ivSAF#		T_EG_SUM
EG_PRED	T	Summary of post-dose values and change from pre-dose of quantitative ECG parameters, by visit	SAF ivSAF#		T_EG_PREDS
EG_QUAL_SUM	T	Summary of qualitative ECG findings, by visit	SAF ivSAF#		T_EG_QUAL
EG_ABN	T	Incidence of ECG abnormalities - QT prolongation, by period	SAF ivSAF#		T_EG_ABN

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.7.13WHO Functional class

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
WHO_SUM	T	Summary of WHO functional class, by visit *[include a best/worst post baseline category]*	SAF ivSAF#		T_WHO_SUM
WHO_CHG	T	Shift table of WHO functional class from baseline to each study visit *[include a shift to worst/best post baseline category]*	SAF ivSAF#		T_WHO_CHG

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set, # Tables will run on SAF only if SAF and ivSAF are identical.

12.8 PK analyses

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PK_CON_SUM_SEL	T	Summary of selexipag plasma concentrations [ng/mL] per time point by dose level and treatment	PKS		T_PK_CON_SUM

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
PK_CON_SUM_ACT	T	Summary of ACT-333679 plasma concentrations [ng/mL] per time point by dose level and treatment	PKS		T_PK_CON_SUM
PK_EP_SUM_SEL	T	Summary of PK endpoints of selexipag by dose level and treatment	PKS	Y	T_PK_EP_SUM
PK_EP_SUM_ACT	T	Summary of PK endpoints of ACT-333679 by dose level and treatment	PKS	Y	T_PK_EP_SUM
PK_SUM_RATIO	T	Summary of PK parameters of ratio ACT-333679/selexipag concentration by dose level and treatment	PKS		T_PK_RATIO_SUM
PK_MM_SEL	T	Mixed model analysis: Ratio of Uptravi and i.v. selexipag period for selexipag by dose level	PKS	Y	T_PK_MM
PK_MM_ACT	T	Mixed model analysis: Ratio of Uptravi and i.v. selexipag period for ACT-333679 by dose level	PKS	Y	T_PK_MM
PK_POW_AUC_SEL	T	Dose proportionality of AUCtau of selexipag after i.v. selexipag: Power model estimation	PKS	Y	T_PK_POW
PK_POW_AUC_SEL	F	Dose proportionality of AUCtau of selexipag after i.v. selexipag: Power model estimation	PKS	Y	F_PK_POW
PK_POW_AUC_ACT	T	Dose proportionality of AUCtau of ACT-333679 after i.v. selexipag: Power model estimation	PKS	Y	T_PK_POW
PK_POW_AUC_ACT	F	Dose proportionality of AUCtau of ACT-333679 after i.v. selexipag: Power model estimation	PKS	Y	F_PK_POW
PK_WIL_SEL	T	Location shift analysis of tmax, ss of selexipag	PKS		T_PK_WIL
PK WIL ACT	T	Location shift analysis of tmax, ss of ACT-333679	PKS		T_PK_WIL

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

12.9 Subject listings

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
SCRF	L	Listing of screening failures	SCR		L_SCRF
PWDS	L	Listing of reasons for premature discontinuation from the study	SAF		L_PWDS
PD	L	Listing of protocol deviations	SCR		L_PD
ANSET	L	Listing of analysis sets	SCR		L_ANSET
PWDT	L	Listing of reasons for premature discontinuation of i.v. selexipag treatment	ivSAF		L_PWDT
DEM	L	Listing of demographics	SCR		L_DEM
BAS	L	Listing of baseline disease characteristics	SCR		L_BAS
MH	L	Listing of medical history	SAF		L_MH
CM	L	Listing of previous and concomitant therapies	SAF		L_CM
CM_PAH_MOD	L	Listing of PAH specific therapies newly started dose changed or stopped during any period. [Add footnote: *Interruptions of Uptravi during i.v. selexipag period as mandated in the protocol are not shown.]*	SAF		L_CM
EXP_PO	L	Listing of Uptravi dosing records	SAF		L_EXP_PO
EXP_IV	L	Listing of study treatment dosing records	ivSAF		L_EXP_IV
COMP	L	Listing of compliance	ivSAF		L_COMP
AE	L	Listing of all adverse events	SCR		L_AE
AE_SCR	L	Adverse events in the Screening Period prior to the first dose of Uptravi on Visit 2 Day 1	SCR		L_AE
AE_DTH	L	Listing of all adverse events leading to death	SAF		L_AE
SAE	L	Listing of all serious adverse events	SAF		L_AE

Output name	Display*	Title (Description)	Analysis set(s)**	Key deliverable	Mock layout
AE_PC	L	Listing of all prostacyclin-associated adverse events	SAF		L_AE
AE_RMP	L	Listing of all adverse events of special interest based on the Uptravi risk management plan [*Replace SOC with Risk category in the Shell. Delete SOC on footnote regarding MedDRA version.*]	SAF		L_AE
AE_INJDET	L	Listing of all injection site reactions	ivSAF		L_AEINJ
AE_PAH	L	Listing of PAH related adverse events	SAF		L_AE
AE_DC	L	Listing of adverse events leading to discontinuation of study treatment	ivSAF		L_AE
AE_REL	L	Listing of adverse events related to study treatment as judged by the investigator	ivSAF		L_AE
LAB	L	Listing of laboratory parameters	SCR		L_LAB
VS	L	Listing of vital signs, body weight and height	SCR		L_VS
EG	L	Listing of quantitative ECG measurements	SAF		L_EG
EG_QUAL	L	Listing of qualitative ECG findings	SAF		L_EG_QUAL
WHO	L	Listing of WHO functional class	SCR		L_WHO
PK_CONC	L	Listing of selexipag / ACT-333679 plasma concentrations	PKS		L_PK_CONC
PK_DER	L	Listing of derived PK parameters of selexipag and ACT-333679	PKS		L_PK_DER
PK_RATIO	L	Listing of Cmax,ss and AUCtau,ss ratio of ACT-333679/selexipag	PKS		L_PK_RATIO
IMP_CONC	L	Listing of selexipag concentration in the infusion solution	PKS		L_IMP_CONC

* T=Summary table, L=Listing, F=Figure, **SCR=Screened analysis set, SAF=Safety analysis set, ivSAF= i.v. Safety analysis set, PKS=Pharmacokinetic analysis set

13 REFERENCES

[D-17.055] AC-065A309: A multicenter, open-label, single-sequence crossover study to assess safety, tolerability and pharmacokinetic of intravenous selexipag in subjects with stable pulmonary arterial hypertension transitioning from an oral stable dose of selexipag. Clinical Study Protocol Version 1. Actelion Pharmaceuticals Ltd; 27 January 2017.

[Gough 1995] Gough K, Hutchinson M, Keene O, Byrom B, Ellis S, Lacey L, et al Assessment of dose proportionality: Report from the statisticians in The Pharmaceutical Industry/Pharmacokinetics UK joint working party. Drug Information Journal. 1995;29:1039–48.

14 APPENDICES

Appendix A Protocol synopsis

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	1. Pregnant, planning to become pregnant or lactating.

CRITERIA	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).

Appendix B 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.
6 If Visit 1 and Visit 2 Day 1 are performed within 7 days, laboratory tests and physical examination 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.
9 Infusion solution samples will be taken from the tubing before each infusion.
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.

Appendix C Discussion and further considerations of the applied statistical methods

Not applicable.

Appendix D Definitions of marked abnormalities and elevated liver function tests

Table 14 Thresholds for marked laboratory abnormalities

Laboratory test name	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100	< 80	Increase of > 20 g/L above baseline	Increase of > 40 g/L above baseline
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) 0.60 (male)	> 0.65
Platelet count (10E9/L)	< 75	< 50	> 600	> 999
Leukocytes (10E9/L)	< 3.0	< 2.0	> 20.0	> 100.0
Neutrophils (10E9/L)	< 1.5	< 1.0	NA	NA
Eosinophils (10E9/L)	NA	NA	> 5.0	NA
Lymphocytes (10E9/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.

Appendix E Mock layout

T_DISP

ACT-293987
Protocol: AC-065A309
Subject disposition
Analysis Set: Screened Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx n (%)	1200-1600 ug N=xxx n (%)	Total N=xxx n (%)
Subjects screened			xxx
Screening failures			xxx
Subjects enrolled in Period 1	xxx (100)	xxx (100)	xxx (100)
Subjects received Uptravi in Period 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects entered in Period 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects received i.v. infusion 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects received i.v. infusion 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects received i.v. infusion 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects completed i.v. selexipag	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects discontinued i.v. selexipag	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects entered in Period 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects completed the study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects discontinued the study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Percentages are based on the number of enrolled subjects.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Display all categories in shell.

T_DISP_COU

ACT-293987
Protocol: AC-065A309
Subject disposition by country and site
Analysis Set: Screened Analysis Set

Country Site Periods	Uptravi b.i.d. dose 200-1000 ug n (%)	 1200-1600 ug n (%)	 Total n (%)
Germany			
All Sites			
Subjects screened			xxx
Screening failures			xxx
Subjects enrolled in Period 1	xxx (100)	xxx (100)	xxx (100)
Subjects received Uptravi in Period 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects entered in Period 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects received i.v. infusion 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects received i.v. infusion 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects received i.v. infusion 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects completed i.v. selexipag	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects discontinued i.v. selexipag	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects entered in Period 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects completed the study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects discontinued the study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Site 1001			
Subjects screened			xxx
Screening failures			xxx
...			

Percentages are based on the number of enrolled subjects.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Include all countries and sites where subjects were enrolled. Display all categories in shell.

T_ANA

ACT-293987
Protocol: AC-065A309
Overview of analysis sets and reasons for exclusion from analysis sets
Analysis Set: Screened Analysis Set

	Uptravi b.i.d. dose 200-1000 ug n (%)	Uptravi b.i.d. dose 1200-1600 ug n (%)	Total n (%)
Screened analysis set			xxx
Safety analysis set	xxx (100)	xxx (100)	xxx (100)
Subjects included in i.v. Safety analysis set	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects excluded from i.v. Safety analysis set	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects included in Pharmacokinetic analysis set	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects excluded from Pharmacokinetic analysis set	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Percentages are based on the Safety analysis set
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Sort reasons for exclusion in descending order of frequency. Display all categories in shell.

T_PWDS

ACT-293987
Protocol: AC-065A309
Reasons for premature discontinuation from the study
Analysis Set: Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx n (%)	1200-1600 ug N=xxx n (%)	Total N=xxx n (%)
Subjects completed the study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects prematurely discontinued the study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subject decision/Withdrawal of consent	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Physician decision	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sponsor decision	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Show all categories written out in the shell in the given order, even if they have zero subjects. Show reason categories as they occurred in descending frequency.

T_PD

ACT-293987
Protocol: AC-065A309
<Table title>
Analysis Set: Screened Analysis Set

Overall

	Total N=xxx n (%)
Subjects with at least one <important> protocol deviation	xxx (xx.x)
<Category 1>	xxx (xx.x)
<Deviation 1>	xxx (xx.x)
<Deviation 2>	xxx (xx.x)
<Deviation 3>	xxx (xx.x)
<Category 2>	xxx (xx.x)
<Deviation 1>	xxx (xx.x)
<Deviation 2>	xxx (xx.x)
<Deviation 3>	xxx (xx.x)
<Category 3>	xxx (xx.x)
<Deviation 1>	xxx (xx.x)
<Deviation 2>	xxx (xx.x)
<Deviation 3>	xxx (xx.x)

A subject may have a deviation in more than one category
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming notes: Repeat with “Germany”, “USA” Show categories as in the PD code list and sort deviations by frequency descending order.

T_DEM

ACT-293987
Protocol: AC-065A309
Summary of baseline demographic characteristics
Analysis Set: Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx	Uptravi b.i.d. dose 1200-1600 ug N=xxx	Total N=xxx
Sex [n (%)]			
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Age [years]			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Age (years) category [n (%)]			
< 18	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
18 - 64	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>= 65	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Height [cm]			
n	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
Body weight [kg]			
n	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
BMI [kg/m^2]			
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Race [n (%)]			
<Race 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Race 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Race 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Race 4>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ethnicity [n (%)]			
<Ethnicity 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Ethnicity 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Country [n (%)]			
<Country 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Country 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

SD = Standard deviation, BMI = Body Mass Index
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Show race, ethnicity and Countries in descending order of frequency. Show ‘Missing’ category only if it occurred.

T_AGECATEU

ACT-293987
Protocol: AC-065A309
EudraCT age categories
Analysis Set: Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx	Uptravi b.i.d. dose 1200-1600 ug N=xxx	Total N=xxx
Age (years) category [n (%)]			
18 - 64	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
65 - 84	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>= 85	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

EudraCT = European union drug regulating authorities clinical trials
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

T_BAS

ACT-293987
Protocol: AC-065A309
Summary of baseline disease characteristics
Analysis Set: Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx	Uptravi b.i.d. dose 1200-1600 ug N=xxx	Total N=xxx
Time since diagnosis of PAH [months]			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx
PAH etiology [n (%)]			
Idiopathic PAH	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Heritable PAH	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Drug or toxin induced PAH	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PAH associated with			
Connective tissue disease	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
HIV infection	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Portal hypertension	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Congenital heart disease	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Schistosomiasis	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Uptravi dose at screening [ug b.i.d.]			
200	xxx (xx.x)		xxx (xx.x)
400	xxx (xx.x)		xxx (xx.x)
600	xxx (xx.x)		xxx (xx.x)
800	xxx (xx.x)		xxx (xx.x)
1000	xxx (xx.x)		xxx (xx.x)
1200		xxx (xx.x)	xxx (xx.x)
1400		xxx (xx.x)	xxx (xx.x)
1600		xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO functional class [n (%)]			
I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Time since diagnosis of PAH is caculated at baseline visit. WHO functional class is assessed on Day 1.
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Show all CRF categories, even if empty. Show 'Missing' category only if it occurred.

T_MH_SOC

ACT-293987
Protocol: AC-065A309
<Table Title>
Analysis Set: Safety Analysis Set

System Organ Class Preferred Term	Uptravi b.i.d. dose 200-1000 ug N=xxx	 1200-1600 ug N=xxx	 Total N=xxx
Subjects with at least one <previous> disease or diagnosis	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<System organ class 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 4>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<System organ class 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 4>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			

System Organ Classes and Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Sort by descending frequency in the SOC and then by descending frequency and then alphabetically in the PTs. Adapt first line in shell (previous/study concomitant).

T_CM

ACT-293987
Protocol: AC-065A309
<Table Title>
Analysis Set: Safety Analysis Set

Period 1: Uptravi, pre-treatment period

ATC Class Preferred Term	Uptravi b.i.d. dose 200-1000 ug N=xxx	 1200-1600 ug N=xxx	 Total N=xxx
Subjects with at least one <ongoing> therapy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<ATC class 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 4>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<ATC class 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 4>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			

Preferred Terms are based on WHO-DRUG dictionary version <xxxx.x>.
The summary does not include PAH-specific therapies.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Sort by descending frequency in the ATC class in total and then by descending frequency and then alphabetically in the PTs. Display Period line only where applicable. Use the following labels for the concomitant medication table:

Analysis Period	**Label in summary table**
Screening	Screening Period
1	Period 1: Uptravi, pre-treatment period
2	Period 2: **i.v. selexipag, treatment period**
3&FU	Period 3: **Uptravi, post-treatment period including safety follow-up period**
1&2	Period 1 & 2: Uptravi, pre-treatment period and i**.v. selexipag treatment period combined**
2&3&FU	Period 2 & 3: **i.v. selexipag, treatment period and Uptravi, post-treatment period including safety follow-up period combined**
1&2&3&FU	Period 1 & 2 & 3: All post-baseline periods including safety follow-up period

Programming note: Use ATC level 4 for ATC class. Sort by descending frequency in the ATC class and then by descending frequency and then alphabetically in the PTs. Modify first line according to table (previous, ongoing, ...).

T_CMPAH

ACT-293987
Protocol: AC-065A309
Summary of ongoing PAH specific therapies at baseline
Analysis Set: Safety Analysis Set

Number of PAH specific therapies PAH medication category Preferred term	Uptravi b.i.d. dose 200-1000 ug N=xxx	 1200-1600 ug N=xxx	 Total N=xxx
Subjects taking Uptravi	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects with at least one additional PAH specific therapy on top of Uptravi	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ERA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PDE5-Inhibitors	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			
ERA + PDE5 Inhibitors	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1> + <Preferred Term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1> + <Preferred Term 3>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...			

Preferred Terms are based on WHO-DRUG dictionary version <xxxx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Use medication categories based on the PAH specific medication search terms. Sort preferred terms by descending order of frequency. Only show categories which are actually occurring. Continue for triplicate therapies, if occurring.

T_EXP_IV

ACT-293987
Protocol: AC-065A309
Exposure to i.v. selexipag
Analysis Set: i.v. Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx	1200-1600 ug N=xxx	Total N=xxx
Number of infusions received [n (%)]			
1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
First infusion			
Planned dose level [ug]			
225 (~ 200 p.o.)	xxx (xx.x)		xxx (xx.x)
450 (~ 400 p.o.)	xxx (xx.x)		xxx (xx.x)
675 (~ 600 p.o.)	xxx (xx.x)		xxx (xx.x)
900 (~ 800 p.o.)	xxx (xx.x)		xxx (xx.x)
1125 (~1000 p.o.)	xxx (xx.x)		xxx (xx.x)
1350 (~1200 p.o.)		xxx (xx.x)	xxx (xx.x)
1575 (~1400 p.o.)		xxx (xx.x)	xxx (xx.x)
1800 (~1600 p.o.)		xxx (xx.x)	xxx (xx.x)
Planned dose [ug]			
n	xx	xx	xx
Mean	xxxx.x	xxxx.x	xxxx.x
SD	xxxx.xx	xxxx.xx	xxxx.xx
Median	xxxx.x	xxxx.x	xxxx.x
Q1, Q3	xxxx.x, xxxx.x	xxxx.x, xxxx.x	xxxx.x, xxxx.x
Min, Max	xxxx, xxxx	xxxx, xxxx	xxxx, xxxx
Actual dose infused [ug]			
n	xx	xx	xx
Mean	xxxx.x	xxxx.x	xxxx.x
SD	xxxx.xx	xxxx.xx	xxxx.xx
Median	xxxx.x	xxxx.x	xxxx.x
Q1, Q3	xxxx.x, xxxx.x	xxxx.x, xxxx.x	xxxx.x, xxxx.x
Min, Max	xxxx, xxxx	xxxx, xxxx	xxxx, xxxx
Actual total time of infusion [minutes]			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Second infusion			
...			
Third infusion			

....
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Show all dose categories even if empty, except the 'Other' category which should only be presented if populated.

T_EXP_PO

ACT-293987
Protocol: AC-065A309
Exposure to Uptravi prior to and after i.v. selexipag
Analysis Set: <Analysis Set>

	Uptravi b.i.d. dose		
	200-1000 ug N=xxx	1200-1600 ug N=xxx	Total N=xxx
Uptravi evening dose before Day 1 [ug]			
200	xxx (xx.x)		xxx (xx.x)
400	xxx (xx.x)		xxx (xx.x)
600	xxx (xx.x)		xxx (xx.x)
800	xxx (xx.x)		xxx (xx.x)
1000	xxx (xx.x)		xxx (xx.x)
1200		xxx (xx.x)	xxx (xx.x)
1400		xxx (xx.x)	xxx (xx.x)
1600		xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not received / missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Uptravi morning dose at Day 1 [ug]			
200	xxx (xx.x)		xxx (xx.x)
400	xxx (xx.x)		xxx (xx.x)
600	xxx (xx.x)		xxx (xx.x)
800	xxx (xx.x)		xxx (xx.x)
1000	xxx (xx.x)		xxx (xx.x)
1200		xxx (xx.x)	xxx (xx.x)
1400		xxx (xx.x)	xxx (xx.x)
1600		xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not received / missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Uptravi evening dose at Day 1 [ug]			
200	xxx (xx.x)		xxx (xx.x)
400	xxx (xx.x)		xxx (xx.x)
600	xxx (xx.x)		xxx (xx.x)
800	xxx (xx.x)		xxx (xx.x)
1000	xxx (xx.x)		xxx (xx.x)
1200		xxx (xx.x)	xxx (xx.x)
1400		xxx (xx.x)	xxx (xx.x)
1600		xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not received / missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Uptravi evening dose at Day 3 [ug]			
200	xxx (xx.x)		xxx (xx.x)
400	xxx (xx.x)		xxx (xx.x)
600	xxx (xx.x)		xxx (xx.x)
800	xxx (xx.x)		xxx (xx.x)
1000	xxx (xx.x)		xxx (xx.x)
1200		xxx (xx.x)	xxx (xx.x)
1400		xxx (xx.x)	xxx (xx.x)
1600		xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not received / missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Show all categories even if empty. The 'Other' and 'Not received/missing' categories shall only be shown if populated.

T_COMPL_IV
ACT-293987
Protocol: AC-065A309
Compliance to i.v. selexipag treatment
Analysis Set: i.v. Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx	Uptravi b.i.d. dose 1200-1600 ug N=xxx	Total N=xxx
First infusion			
Compliance [%]			
n	xx	xx	xx
Mean	xxxx.x	xxxx.x	xxxx.x
SD	xxxx.xx	xxxx.xx	xxxx.xx
Median	xxxx.x	xxxx.x	xxxx.x
Q1, Q3	xxxx.x, xxxx.x	xxxx.x, xxxx.x	xxxx.x, xxxx.x
Min, Max	xxxx, xxxx	xxxx, xxxx	xxxx, xxxx
Second infusion			
Compliance [%]			
n	xx	xx	xx
Mean	xxxx.x	xxxx.x	xxxx.x
SD	xxxx.xx	xxxx.xx	xxxx.xx
Median	xxxx.x	xxxx.x	xxxx.x
Q1, Q3	xxxx.x, xxxx.x	xxxx.x, xxxx.x	xxxx.x, xxxx.x
Min, Max	xxxx, xxxx	xxxx, xxxx	xxxx, xxxx
Third infusion			
Compliance [%]			
n	xx	xx	xx
Mean	xxxx.x	xxxx.x	xxxx.x
SD	xxxx.xx	xxxx.xx	xxxx.xx
Median	xxxx.x	xxxx.x	xxxx.x
Q1, Q3	xxxx.x, xxxx.x	xxxx.x, xxxx.x	xxxx.x, xxxx.x
Min, Max	xxxx, xxxx	xxxx, xxxx	xxxx, xxxx
Overall			
Compliance [%]			
n	xx	xx	xx
Mean	xxxx.x	xxxx.x	xxxx.x
SD	xxxx.xx	xxxx.xx	xxxx.xx
Median	xxxx.x	xxxx.x	xxxx.x
Q1, Q3	xxxx.x, xxxx.x	xxxx.x, xxxx.x	xxxx.x, xxxx.x
Min, Max	xxxx, xxxx	xxxx, xxxx	xxxx, xxxx

Subject with missing infusions have compliance zero.
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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T_EXP_ADJ

ACT-293987
Protocol: AC-065A309
Summary of study treatment administration, reasons for interruptions and end of infusion
Analysis Set: i.v. Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx	1200-1600 ug N=xxx	Total N=xxx
First infusion			
Not received [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Temporary interruptions [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Due to an AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not due to an AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
End of infusion [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Premature discontinuation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Completed as per protocol	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Second infusion			
Not received [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Temporary interruptions [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Due to an AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not due to an AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
End of infusion [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Premature discontinuation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Completed as per protocol	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Third infusion			
Not received [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Temporary interruptions [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Due to an AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not due to an AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
End of infusion [n (%)]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Premature discontinuation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Completed as per protocol	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Subjects may have more than one interruption but are counted only once in each category.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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T_PWDT
ACT-293987
Protocol: AC-065A309
Reasons for premature discontinuation of i.v. selexipag treatment
Analysis Set: i.v. Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx n (%)	Uptravi b.i.d. dose 1200-1600 ug N=xxx n (%)	Total N=xxx n (%)
Subjects completed i.v. selexipag treatment	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects prematurely discontinued i.v. selexipag treatment	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Death	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Pre-specified discontinuation criteria	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subject decision	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Physician decision	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sponsor decision	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Reason 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Show all categories written out in the shell in the given order, even if they have zero subjects. Show reason categories as they occurred in descending frequency.

T_AE_SOC
ACT-293987
Protocol: AC-065A309
<Table title>
Analysis Set: <Analysis set>

Period 1: Uptravi, pre-treatment period

	Uptravi b.i.d. dose					
	200-1000 ug N=xxx		1200-1600 ug N=xxx		Total N=xxx	
System Organ Class Preferred Term	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Subjects with at least one AE	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<System organ class 1>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 1>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 2>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 3>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 4>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<System organ class 2>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 1>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 2>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 3>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 4>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
...						

CI = Confidence interval
System Organ Classes and Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Sort by descending frequency in the SOC in total and then by descending frequency and then alphabetically in the PTs. Use the following labels:

Analysis Period	**Label in summary table**
1	Period 1: Uptravi, pre-treatment period
2	Period 2: **i.v. selexipag, treatment period**
3&FU	Period 3: **Uptravi, post-treatment period including safety follow-up period**
1&2	Period 1 & 2: Uptravi, pre-treatment period and i.**v. selexipag treatment period combined**
2&3&FU	Period 2 & 3: **i.v. selexipag, treatment period and Uptravi, post-treatment period including safety follow-up period combined**
1&2&3&FU	Period 1 & 2 & 3: All post-baseline periods including safety follow-up period

T_AE_SOC2
ACT-293987
Protocol: AC-065A309
<Table title>
Analysis Set: <Analysis set>

MedDRA System organ class Preferred term	Uptravi b.i.d. dose 200-1000 ug N=xxx Subjects n (%)	 Events n	 1200-1600 ug N=xxx Subjects n (%)	 Events n	 Total N=xxx Subjects n (%)	 Events n
Subjects with at least one event	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<System organ class 1>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 1>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 2>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 3>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 4>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<System organ class 2>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 1>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 2>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 3>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
<Preferred term 4>	xxx (xx.x)	xxx	xxx (xx.x)	xxx	xxx (xx.x)	xxx
...						

System Organ Classes and Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Table shell for EudraCT/ClinicalTrails.gov disclosure. See Section 7.2.2.1 of the SAP.

T_AE_PT

ACT-293987
Protocol: AC-065A309
<Table title>
Analysis Set: <Analysis set>

Period 1: Uptravi, pre-treatment period

	Uptravi b.i.d. dose					
	200-1000 ug N=xxx		1200-1600 ug N=xxx		Total N=xxx	
Preferred term	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Subjects with at least one AE	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 1>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 2>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 3>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 4>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 5>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 6>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 7>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
<Preferred term 8>	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x	xxx (xx.x)	xx.x, xx.x
...						

CI = Confidence interval
Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Sort by descending frequency and then alphabetically in the PTs in total. Use the following labels:

Analysis Period	**Label in summary table**
1	Period 1: Uptravi, pre-treatment period
2	Period 2: **i.v. selexipag, treatment period**
3&FU	Period 3: **Uptravi, post-treatment period including safety follow-up period**
1&2	Period 1 & 2: Uptravi, pre-treatment period and i.**v. selexipag treatment period combined**
2&3&FU	Period 2 & 3: **i.v. selexipag, treatment period and Uptravi, post-treatment period including safety follow-up period combined**
1&2&3&FU	Period 1 & 2 & 3: All post-baseline periods including safety follow-up period

T_AE_PT_INT

ACT-293987
Protocol: AC-065A309
Incidence of adverse events by preferred term and maximum intensity
Analysis Set: <Analysis set>

Preferred Term Intensity	Uptravi b.i.d. dose 200-1000 ug N=xxx n (%)	 1200-1600 ug N=xxx n (%)	 Total N=xxx n (%)
Subjects with at least one AE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 1>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Preferred term 2>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

The maximum intensity of the AE is shown.
All post-baseline AEs are shown (Period 1 & 2 & 3 including safety follow-up)
Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Sort by descending frequency and then alphabetically in the PTs. Show missing category only if it occurred in the data.

T_AEINJ

ACT-293987
Protocol: AC-065A309
Grade and diagnosis criteria of injection site reactions
Analysis Set: i.v. Safety Analysis Set

	Uptravi b.i.d. dose 200-1000 ug N=xxx n (%)	1200-1600 ug N=xxx n (%)	Total N=xxx n (%)
Subjects with at least one injection site reaction	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subjects with at least one clinically significant injection site reaction	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Worst Grade			
Mild	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Moderate	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Potentially life threatening	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Criteria			
Pain	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Tenderness	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Erythema/redness	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Swelling	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Induration	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Injection site hemorrhage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

The worst grade of all injection site reactions was counted in a subject.
A subject may have more than one diagnosis criterion.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: For each subject, display the worst grade of all injection site reactions. Display each subject once for all diagnosis criteria reported in a subject.

T_LB_SUM

ACT-293987
Protocol: AC-065A309
<Table Title>
Analysis Set: Safety Analysis Set

Parameter: Haemoglobin [g/L]

Treatment group / Time point	Baseline n	Baseline Mean	Baseline SD	Baseline Median	Baseline Min	Baseline Max	Time Point Mean	Time Point SD	Time Point Median	Time Point Min	Time Point Max	Change from baseline Mean	Change from baseline SD	Change from baseline Median	Change from baseline Min	Change from baseline Max
Uptravi b.i.d. dose 200-1000 ug (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Uptravi b.i.d. dose 1200-1600 ug (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Total (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx

Baseline is the Day 1 assessment or last assessment prior to Day 1.
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for all Hematology/Clinical chemistry parameters as stated in Section 7.4 of the SAP.

T_LB_ABN

ACT-293987
Protocol: AC-065A309
Incidence of marked laboratory values, by period
Analysis Set: Safety Analysis Set

Period 2: i.v. selexipag, treatment period

Category Parameter	Grade	Severity of abnormality	Uptravi b.i.d. dose 200-1000 ug N = xxx n / m (%)	 1200-1600 ug N = xxx n / m (%)	 Total N = xxx n / m (%)
Hematology					
Hemoglobin	LL	< 100 g/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 80 g/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	Increase > 20 g/L above baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	Increase > 40 g/L above baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Hematocrit	LL	< 0.28 L/L [f], < 0.32 L/L [m]	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 0.2 L/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	> 0.55 L/L [f], > 0.60 L/L [m]	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 0.65 L/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Platelet count	LL	< 75 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 50 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	> 600 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 999 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Leukocytes	LL	< 3.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 2.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	> 20.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 100.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Neutrophils	LL	< 1.5 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 1.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Eosinophils	HH	> 5.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Lymphocytes	LL	< 0.8 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 0.5 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	> 4.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)

	HHH	> 20.0 x10^9/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Biochemistry					
ALT	HH	> 3 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 5 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
AST	HH	> 3 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 5 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Alkaline phosphatase	HH	> 2.5 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 5 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Total bilirubin	HH	> 2 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 5 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Creatinine	HH	> 1.5 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 3 xULN	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Sodium	LLL	< 130 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	> 150 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 155 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Potassium	LL	< 3.2 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	LLL	< 3.0 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	> 5.5 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HHH	> 6.0 mmol/L	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)

ULN = Upper limit of normal. Subjects are summarized in each category they fall into.
n = Subjects with event, m = Subjects with assessment in the specified time period (at risk)
Post-baseline abnormalities not present at baseline or abnormalities worsening after baseline are shown.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Use the following labels:

Analysis Period	**Label in summary table**
1	Period 1: Uptravi, pre-treatment period
2	Period 2: **i.v. selexipag, treatment period**
3&FU	Period 3: **Uptravi, post-treatment period including safety follow-up period**
2&3&FU	Period 2 & 3: **i.v. selexipag, treatment period and Uptravi, post-treatment period including safety follow-up period combined**

T_VS_SUM

ACT-293987
Protocol: AC-065A309
Summary and change from baseline of vital signs, by visit
Analysis Set: Safety Analysis Set

Parameter: Systolic blood pressure [mmHg]

Treatment group / Time point		Baseline					Time Point					Change from baseline				
	n	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Uptravi b.i.d. dose 200-1000 ug (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 2 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+25 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+87 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 4 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 6 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 8 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+12 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 3 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+25 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+87 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 4 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 6 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 8 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+12 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Uptravi b.i.d. dose 1200-1600 ug (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 2 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
...	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx

Baseline is the Day 1 assessment or last assessment prior to Day 1.
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for Total. Then repeat for DBP and pulse.

T_VS_PREDS

ACT-293987
Protocol: AC-065A309
Summary of post-dose values and change from pre-dose of vital signs, by visit
Analysis Set: Safety Analysis Set

Parameter: Systolic blood pressure [mmHg]

Treatment group / Time point	n	Pre-dose (+0 h) Mean	SD	Median	Min	Max	Time Point Mean	SD	Median	Min	Max	Change from pre-dose Mean	SD	Median	Min	Max
Uptravi b.i.d. dose 200-1000 ug (N=xxx)																
Visit 2 Day 2 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
+25 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+87 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 4 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 6 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 8 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+12 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 3 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
+25 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+87 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 4 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 6 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 8 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+12 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Uptravi b.i.d. dose 1200-1600 ug (N=xxx)																
Visit 2 Day 2 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
+25 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+87 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 4 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 6 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 8 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+12 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 3 + 0 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
+25 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+87 min	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 4 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 6 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+ 8 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
+12 h	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx

SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for Total. Repeat for DBP and pulse. Show only visits where pre-/post-dose assessments were conducted (Visit 2 Day 2 and Visit 2 Day 3).

T_VS_ABN

ACT-293987
Protocol: AC-065A309
Incidence of marked blood pressure abnormalities, by period
Analysis Set: Safety Analysis Set

Period 2: i.v. selexipag treatment period

			Uptravi b.i.d. dose 200-1000 ug N = xxx n / m (%)	1200-1600 ug N = xxx n / m (%)	Total N = xxx n / m (%)
Supine SBP [mmHg]	L	SBP < 90	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
		SBP decrease > 40 from baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	H	140 <= SBP <= 159	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
		SBP increase > 20 from baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	SBP >= 160	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Supine DBP [mmHg]	L	DBP < 50	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
		DBP decrease > 20 from baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	H	90 <= DBP <= 99	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
		DBP increase > 20 from baseline	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
	HH	DBP >= 100	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)

SBP = Systolic blood pressure, DBP = Diastolic blood pressure
n = Subjects with event, m = Subjects with assessment in the specified time period (at risk)
Post-baseline abnormalities not present at baseline or abnormalities worsening after baseline are shown.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Use the following labels:

Analysis Period	Label in summary table
1	Period 1: Uptravi, pre-treatment period
2	Period 2: **i.v. selexipag, treatment period**
3&FU	Period 3: **Uptravi, post-treatment period including safety follow-up period**
2&3&FU	Period 2 & 3: **i.v. selexipag, treatment period and Uptravi, post-treatment period including safety follow-up period combined**

T_EG_SUM

ACT-293987
Protocol: AC-065A309
Summary and change from baseline of quantitative ECG parameters, by visit
Analysis Set: Safety Analysis Set

Parameter: ECG Mean heart rate [bpm]

Treatment group		Baseline						Time Point					Change from baseline				
Time point	n	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Uptravi b.i.d. dose 200-1000 ug (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 2 IV-1 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
IV-1 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 2 IV-2 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
IV-2 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 3 IV-3 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
IV-3 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 3	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Uptravi b.i.d. dose 1200-1600 ug (N=xxx)																
Baseline	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
Visit 2 Day 2 IV-1 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
IV-1 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
...	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx

Baseline is the Day 1 assessment or last assessment prior to Day 1.
pre = pre-dose assessment prior to infusion, post = post dose assessment (within 30 minutes after end of infusion)
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for Total. Then repeat for PR Interval Single Beat [msec]; QRS Duration, Single Beat [msec]; QT Interval, Single Beat [msec]; QTcB Interval, Single Beat [msec]; QTcF Interval, Single Beat [msec].

T_EG_PREDS

ACT-293987
Protocol: AC-065A309
Summary of post-dose values and change from pre-dose of quantitative ECG parameters, by visit
Analysis Set: Safety Analysis Set

Parameter: ECG Mean heart rate [bpm]

Treatment group		Pre-dose					Time Point					Change from pre-dose				
Time point	n	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Uptravi b.i.d. dose 200-1000 ug (N=xxx)																
Visit 2 Day 2 IV-1 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
IV-1 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 2 IV-2 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
IV-2 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Visit 2 Day 3 IV-3 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
IV-3 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
Uptravi b.i.d. dose 1200-1600 ug (N=xxx)																
Visit 2 Day 2 IV-1 pre	xx	xxx.x	xx.xx	xxx.x	xxx	xxx										
IV-1 post	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx
...	xx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx	xxx.x	xx.xx	xxx.x	xxx	xxx

pre = pre-dose assessment prior to infusion, post = post dose assessment (within 30 minutes after end of infusion)
SD = Standard deviation
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Continue for Total. Then repeat for PR Interval Single Beat [msec]; QRS Duration, Single Beat [msec]; QT Interval, Single Beat [msec]; QTcB Interval, Single Beat [msec]; QTcF Interval, Single Beat [msec].

T_EG_ABN

ACT-293987
Protocol: AC-065A309
Incidence of ECG abnormalities - QT prolongation, by period
Analysis Set: Safety Analysis Set

Period 2: i.v. selexipag treatment period

	Uptravi b.i.d. dose		
	200-1000 ug N=xxx	1200-1600 ug N=xxx	Total N=xxx
Parameter	n / m (%)	n / m (%)	n / m (%)
QTc (Bazett's correction), [msec]			
Value > 450 #	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 480 #	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 500 #	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Increase from baseline > 30	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Increase from baseline > 60	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 450 and increase from baseline > 30	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 450 and increase from baseline > 60	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
QTc (Fridericia's correction), [msec]			
Value > 450 #	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 480 #	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 500 #	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Increase from baseline > 30	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Increase from baseline > 60	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 450 and increase from baseline > 30	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Value > 450 and increase from baseline > 60	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)

n = Subjects with event, m = Subjects with QTc evaluation (at risk)
# Baseline value below treshold OR baseline value above treshold and post baseline value worsened (increased)
If more than one ECG in a period has the same abnormality category, the subject is counted only once.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Use the following labels:

Analysis Period	Label in summary table
1	Period 1: Uptravi, pre-treatment period
2	Period 2: **i.v. selexipag, treatment period**
3&FU	Period 3: **Uptravi, post-treatment period including safety follow-up period**
2&3&FU	Period 2 & 3: **i.v. selexipag, treatment period and Uptravi, post-treatment period including safety follow-up period combined**

T_EG_QUAL

ACT-293987
Protocol: AC-065A309
Summary of qualitative ECG findings, by visit
Analysis Set: Safety Analysis Set

Visit Interpreation Finding	Uptravi b.i.d. dose 200-1000 ug N=xxx n / m (%)	 1200-1600 ug N=xxx n / m (%)	 Total N=xxx n / m (%)
Baseline/Visit 2 Day 1			
Normal	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Unable to interpret	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Abnormal	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 1>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 2>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 3>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 4>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Visit 2 Day 2 IV-1 pre			
Normal	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Unable to interpret	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Abnormal	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 1>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 2>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 3>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
<Finding 4>	xxx / xxx (xx.x)	xxx / xxx (xx.x)	xxx / xxx (xx.x)
Visit 2, Day 2 IV-1 post			
...			
Any time post baseline			
...			

Baseline is the Day 1 assessment or last assessment prior to Day 1.
pre = pre-dose assessment prior to infusion, post = post doase assessment (within 30 minutes after end of infusion)
n = Subjects with event, m = Subjects with qualitative evaluation (at risk in category)
Findings not present at baseline are shown at post baseline timepoints.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy

Program: /<folder>/<program_name>.sas
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Programming note: Continue for all scheduled ECG assessments (Visit 2 Day 2 IV-2 pre/post, Visit 2 Day 3 IV3 pre/post, Visit 3) and for any time post baseline. Sort abnormalities by descending total incidence.

T_WHO_SUM

ACT-293987
Protocol: AC-065A309
Summary of WHO functional class, by visit
Analysis Set: Safety Analysis Set

Visit WHO functional class	Uptravi b.i.d. dose 200-1000 ug N=xxx n (%)	 1200-1600 ug N=xxx n (%)	 Total N=xxx n (%)
Baseline			
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Visit 2 Day 3			
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Visit 3			
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Worst post baseline (including unscheduled visits)			
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Best post baseline (including unscheduled visits)			
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Baseline is the Day 1 assessment or last assessment prior to Day 1.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: The missing category will only be presented if occurring in the data.

T_WHO_CHG

ACT-293987
Protocol: AC-065A309
Shift table of WHO functional class from baseline to each study visit
Analysis Set: Safety Analysis Set

Treatment group: Uptravi b.i.d. dose 200-1000 ug (N=xxx)

	Baseline				
Visit WHO functional class	WHO FC I n (%)	WHO FC II n (%)	WHO FC III n (%)	WHO FC IV n (%)	Missing n (%)
Visit 2 Day 3					
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Visit 3					
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Worst post-baseline (including unscheduled visits)					
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Best post-baseline (including unscheduled visits)					
WHO FC I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC III	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
WHO FC IV	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Baseline is the Day 1 assessment or last assessment prior to Day 1.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: The missing category will only be presented if occurring in the data. Repeat for Dose >=1200 ug and total groups.

T_PK_CON_SUM

ACT-293987
Protocol: AC-065A309
Summary of <selexipag/ACT-333679> plasma concentrations [ng/mL] per time point by dose level and treatment
Analysis Set: Pharmacokinetic Analysis Set

Dose group: 200 ug b.i.d. p.o./ 225 ug b.i.d. i.v.

Treatment Time point	n	Arithmetic mean (95% CI)	Geometric mean (95% CI)	SD	SE	Min	Median	Max
Uptravi								
0 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
1 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
2 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
4 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
6 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
8 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
12 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
i.v. selexipag								
0 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
25 min	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
87 min	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
4 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
6 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
8 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx
12 h	xxx	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)	xxx	xxx	xxx	xxx	xxx

CI = Confidence interval, SD = Standard deviation, SE = Standard error, p.o. = per os, b.i.d. = twice daily; i.v. = intravenous
Implausible plasma concentrations are not included in the summary.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for dose groups 400p.o./450i.v., 600p.o./675i.v., 800p.o./900i.v., 1000p.o./1125i.v., 1200p.o./1350i.v., 1400p.o./1575i.v., 1600p.o./1800i.v., and dose normalized.

T_PK_EP_SUM

ACT-293987
Protocol: AC-065A309
Summary of PK parameters of <selexipag/ACT-333679> by dose level and treatment
Analysis Set: Pharmacokinetic Analysis Set

Dose level: 200 ug b.i.d. p.o./ 225 ug b.i.d. i.v.

PK parameter Statistic	Uptravi N=xxx	i.v. selexipag N=xxx
Subjects in dose level	xxx	xxx
AUCtau,ss [ng.h/mL]		
N	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
Geometric mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
SD	xx.x	xx.x
SE	xxx	xxx
CV%	xx.x	xx.x
CV ln%	xx.x	xx.x
Median	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x
Ctrough,ss, 0h [ng/mL]		
n	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
Geometric mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
SD	xx.x	xx.x
SE	xxx	xxx
CV%	xx.x	xx.x
CV ln%	xx.x	xx.x
Median	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x
Ctrough,ss, 12h [ng/mL]		
n	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
Geometric mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
SD	xx.x	xx.x
SE	xxx	xxx
CV%	xx.x	xx.x
CV ln%	xx.x	xx.x
Median	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x
Cmax,ss [ng/mL]		
n	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
Geometric mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
SD	xx.x	xx.x
SE	xxx	xxx
CV%	xx.x	xx.x
CV ln%	xx.x	xx.x
Median	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x
tmax,ss [h]		
n	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
SD	xx.x	xx.x
SE	xxx	xxx
CV w%	xx.x	xx.x
Median	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x

CI = Confidence interval, SD = Standard deviation, SE = Standard error, CV% = Coefficient of variation [%], CV_b% = Between-subject coefficient of variation [%], CV_ln% = Coefficient of variation of logarithmized values [%], p.o. = per os, b.i.d. = twice daily, i.v. = intravenous
Values obtained from implausible plasma concentrations are not included in the summary.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for dose all dose levels and dose normalized.

T_PK_RATIO_SUM

ACT-293987
Protocol: AC-065A309
Summary of PK parameters of ratio ACT-333679/selexipag concentration by dose level and treatment
Analysis Set: Pharmacokinetic Analysis Set

Dose level: 200 ug b.i.d. p.o./ 225 ug b.i.d. i.v.

PK parameter Statistic	Uptravi N=xxx	i.v. selexipag N=xxx
Subjects in dose level	xxx	xxx
AUCtau,ss [ng.h/mL]		
N	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.xx, xx.xx)	xxx (xx.xx, xx.xx)
Geometric mean (95% CI)	xxx (xx.xx, xx.xx)	xxx (xx.xx, xx.xx)
SD	xx.xxx	xx.xxx
SE	xx.xxx	xx.xxx
CV%	xx.xx	xx.xx
CV ln%	xx.xx	xx.xx
Median	xx.xx	xx.xx
Min, Max	xx.xx, xx.xx	xx.xx, xx.xx
Cmax,ss [ng/mL]		
n	xxx	xxx
Arithmetic mean (95% CI)	xxx (xx.xx, xx.xx)	xxx (xx.xx, xx.xx)
Geometric mean (95% CI)	xxx (xx.xx, xx.xx)	xxx (xx.xx, xx.xx)
SD	xx.xxx	xx.xxx
SE	xx.xxx	xx.xxx
CV%	xx.xx	xx.xx
CV ln%	xx.xx	xx.xx
Median	xx.xx	xx.xx
Min, Max	xx.xx, xx.xx	xx.xx, xx.xx

CI = Confidence interval, SD = Standard deviation, SE = Standard error, CV% = Coefficient of variation (SD/mean) [%], CV_ln% = Coefficient of variation of logarithmized values, [%] p.o. = per os, b.i.d. = twice daily; i.v.= intravenous
Values obtained from implausible plasma concentrations are not included in the summary.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Continue for dose all dose levels and dose normalized.

T_PK_MM

ACT-293987
Protocol: AC-065A309
Mixed model analysis: Ratio of Uptravi and i.v. selexipag period for <selexipag/ACT-333679> by dose level
Analysis Set: Pharmacokinetic Analysis Set

Endpoint Statistic	Cmax,ss	AUCtau ss
Dose level: 200 ug b.i.d. p.o./ 225 ug b.i.d. i.v.		
n	xxx	xxx
Ratio of geom. means (i.v./p.o)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
90% CI	x.xxx, x.xxx	x.xxx, x.xxx
CV b[%]	xx.xx	xx.xx
Dose level: 400 ug b.i.d. p.o./ 450 ug b.i.d. i.v.		
n	xxx	xxx
Ratio of geom. means (i.v./p.o)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
90% CI	x.xxx, x.xxx	xxx (xx.x, xx.x)
CV b[%]	xx.x	xx.x
Dose level: ...		
n	xxx	xxx
Ratio of geom. means (i.v./p.o)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
90% CI	x.xxx, x.xxx	xxx (xx.x, xx.x)
CV b[%]	xx.x	xx.x
...		
Dose level: Normalized dose (200 ug)		
n	xxx	xxx
Ratio of geom. means (i.v./p.o)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
90% CI	x.xxx, x.xxx	xxx (xx.x, xx.x)
CV b[%]	xx.x	xx.x

CI = Confidence interval, n.e. = not estimable. p.o. = per os, b.i.d. = twice daily; i.v. = intravenous
Geometric mean ratios were obtained by computing the anti-log of the treatment group difference of a mixed model with treatment as fixed and subject as random effect to the log-transformed data. CV_b[%] was computed using the mean squared error or residuals as a measure of variation.
Values obtained from implausible plasma concentrations are not included in the analysis.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Display all dose levels. For dose levels not sufficiently populated to allow an estimation populate only 'n' row and show 'n.e.' for the remaining statistics.

T_PK_POW

ACT-293987
Protocol: AC-065A309
Dose proportionality of AUCtau of <selexipag/ACT-333679> after i.v. selexipag: Power model estimation
Analysis Set: Pharmacokinetic Analysis Set

n	beta	SE(beta)	90% CI
xxx	x.xxx	xx.xxxx	x.xxx, x.xxx

CI = Confidence interval
Dose proportionality will be assumed if beta is close to 1, i.e., if the CI of beta includes 1.
Values obtained from implausible plasma concentrations are not included in the analysis.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Produce table only if sufficient subjects are included in at least three dose levels.

T_PK_WIL
ACT-293987
Protocol: AC-065A309
Location shift analysis of tmax, ss of <selexipag/ACT-333679>
Analysis Set: Pharmacokinetic Analysis Set

	i.v. selexipag - Uptravi		
n	Median	90% CI	p-value
xxx	x.xxx	x.xxx, x.xxx	x.xxxx

CI = Confidence interval from a Hodges - Lehmann estimation.
p-value is derived from a Wilcoxon signed rank test.
Values obtained from implausible plasma concentrations are not included in the analysis.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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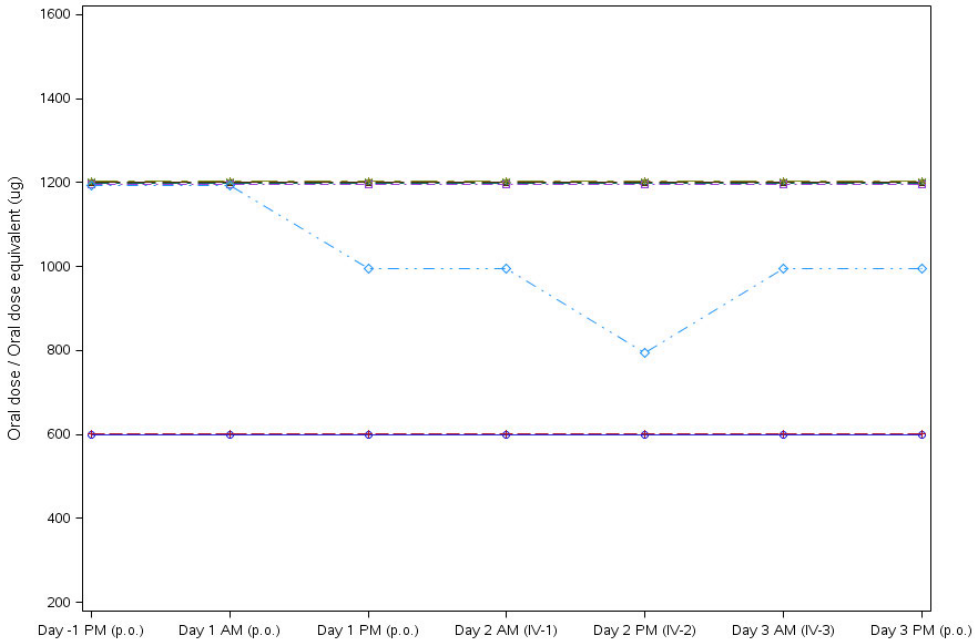
F_EXP

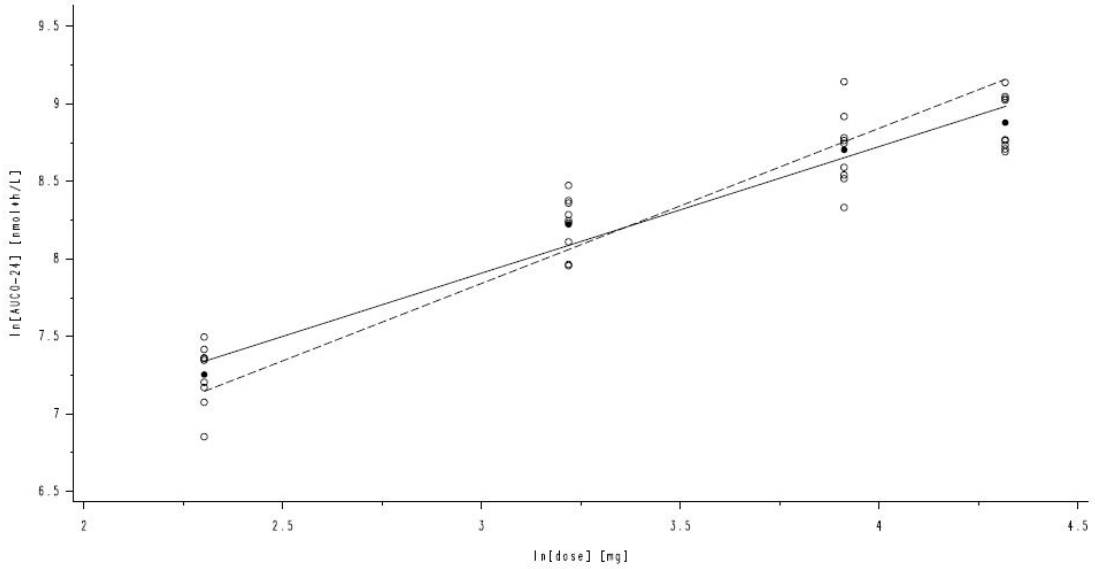
ACT-293987
Protocol: AC-065A309
Shift in selexipag dose between oral and i.v. treatment
Analysis Set: i.v. Safety Analysis Set



Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: This is just a conceptual graphic showing subjects from two dose levels (there will be more levels in the study). Adapt to Actelion standards. Jitter series plots such that individual subject lines are clearly visible. Do use color for each series plot.

F_PK_POW
ACT-293987
Protocol: AC-065A309
Dose proportionality of AUCtau <selexipag/ACT-333679> after i.v. selexipag: Power model estimation
Analysis Set: Pharmacokinetic Analysis Set



Values obtained from implausible plasma concentrations are not included in the analysis.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: This is just a general sketch: Display log dose vs. log AUC and display a regression line from the model with the slope of estimated beta. Add a second line with beta (i.e., slope) =1 as reference.

L_SCRF

ACT-293987
Protocol: AC-065A309
Listing of screening failures
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Date	Reason for screening failure
1001001	ddMMMyyyy	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
1001002	ddMMMyyyy	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: Add specification for reason of screening failure, if available from the database.

L_PWDS

ACT-293987
Protocol: AC-065A309
Listing of reasons for premature discontinuation from the study
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Status	Date / Day	Reason for discontinuation from the study	Details
1001001	Completed	ddMMMyyy / xxx		
1001002	Discontinued	ddMMMyyy / xxx	Death	
1001003	Discontinued	ddMMMyyy / xxx	Physician decision	xxxx xxxxxxxx

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_PHYS

ACT-293987
Protocol: AC-065A309
Listing of physical examination results
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Visit	Date / Day	Body system	Result	Specify abnormality	Clin. sign.
1001001	Screening	ddMMMyyy / xxx	General appearance	Normal		
			Head, ears, eyes, nose, throat	Abnormal	XXXXXXXXXX	No
			...			
	Visit 2 - Day 1	ddMMMyyy / xxx	...			
	Visit 3	ddMMMyyy / xxx				

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Display ‘not done’ in the result section if a specific physical examination was databased as such.

L_PWDT

ACT-293987
Protocol: AC-065A309
Listing of reasons for premature discontinuation of i.v. selexipag treatment
Analysis Set: i.v. Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Status	Reason for discontinuation of i.v. selexipag treatment	Details
1001001	Completed		
1001002	Discontinued	Death	
1001003	Discontinued	Physician decision	xxxx xxxxxxxx

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_AE

ACT-293987
Protocol: AC-065A309
Listing of <Listing title>
Analysis Set: <Analysis set>

Country: <country>, Site: <Site number>

Subject number	System Organ Class Preferred Term (Reported Term)	Start date/ time/Day	End date/ time/Day	Duration (days)	Serious	Ser. crit.	Intensity	Concom. trt. given	Action taken i.v. selexipag	Related to i.v. selexipag	Outcome
1001001	xxxxxxxxxxxxxxxxxx XXXXXXXXXXXXXXX (XXX XXX XXXX)	ddMMMyyyy/ hh:mm/xx	ddMMMyyyy/ hh:mm/xx	xx	Y	2,3	sev	Y	6	Y	Revcovered/ Resolved
1001002	xxxxxxxxxxxxxxxxxx XXXXXXXXXXXXXXX (XXX XXX XXXX)§	ddMMMyyyy/ hh:mm/xx	ddMMMyyyy/ hh:mm/xx	xx	N		mod	N	6	N	Revcovering/ Resolving

§ = Injection site reaction adverse event
Seriousness criteria: 1 Death, 2 Life-threatening, 3 Results in significant disability, 4 Birth defect/congenital anomaly, 5 Required/Prolonged hospitalization, 6 Other medical importance
Action taken with i.v. selexipag: 1 Dose not changed, 2 Dose increased, 3 Dose reduced, 4 Drug interrupted, 5 Drug withdrawn, 6 Not applicable, 7 Unknown
Intensity: mild = Mild, mod = Moderate, sev = Severe
System Organ Classes and Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_DTH

ACT-293987
Protocol: AC-065A309
Listing of all deaths
Analysis Set: Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Death Date / Time / Day	Primary cause of death (Reported term)
1001002	ddMMMyyy / hh:mm / xxx	XXXXXXXX (XXXXXXXXXXXXXXXXXXX)

Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_AEINJ

ACT-293987
Protocol: AC-065A309
Listing of all injection site reactions
Analysis Set: i.v. Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Onset Date / Time / Day	Resolution Date / Time / Day	Criteria	Grade	Clinically Significant	Adverse event Preferred Term
1001002	ddMMMyyy / hh:mm / xxx	ddMMMyyy / hh:mm / xxx	Swelling	Moderate	Y	XXXXXXXXX
	ddMMMyyy / hh:mm / xxx	ddMMMyyy / hh:mm / xxx	Pain	Mild	N	

Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_LAB

ACT-293987
Protocol: AC-065A309
Listing of laboratory parameters
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Parameter [SI Unit]	Visit	Study Day	Value	Reference Range	Change from baseline Absolute	Change from baseline Percent
1001002	Hemoglobin [g/L]	Screening		xxxx	xxx - xxx	xxx	xxx
		Unscheduled		xxxx H	xxx - xxx	xxx	xxx
		Unscheduled		xxxx$	xxx - xxx	xxx	xxx
		Visit 2 - Day 1		xxxx*HH	xxx - xxx	xxx	xxx

* = Baseline, H = Above upper limit of normal range, L = Below lower limit of normal range (as flagged by the laboratory)
$ = Local lab value, not used for summary tables
HH, HHH: Marked abnormally high values, LL, LLL: Marked abnormally low values (derived using SI units)
Newly occurring or worsening post-baseline marked abnormalities are flagged.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_VS

ACT-293987
Protocol: AC-065A309
Listing of vital signs, body weight and height
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Parameter [SI Unit]	Visit	Study Day	Time point	Value	Change from baseline
1001002	Systolic blood pressure [mmHg]	Screening	xx		xxxx	xxxxx
		Visit 2 - Day 1	xx	Pre dose	xxxx*	xxxxx
				+ 25 min	xxxxHH	xxxx
				+ 87 min	xxxx	xxxxx
				+ 4 h	xxxx	xxxx

* = Baseline, HH: Marked abnormally high values, LL: Marked abnormally low values
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
Newly occurring or worsening post-baseline marked abnormalities are flagged.
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_PD

ACT-293987
Protocol: AC-065A309
Listing of protocol deviations
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Category	Identifier	Description	Exclusion from PKS	Important PD
1001002	Screening period	000	XXXXXXXXXXXXXXXX	Yes	Yes
	Treatment and observation period	000	YYYYYYYYYYYYYYYY	No	No

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_ANSET

ACT-293987
Protocol: AC-065A309
Listing of analysis sets
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Screened analysis set (SCR)	Safety analysis set (SAF)	i.v. Safety analysis set (ivSAF)	Pharmacokinetic analysis set (PKS)	Reason
1001001	Yes	No	No	No	Not treated with i.v. selexipag
1001002	Yes	Yes	Yes	No	XXXXX

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_DEM

ACT-293987
Protocol: AC-065A309
Listing of demographics
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Age [years]	Sex	Race	Ethnicity	Weight [kg]	Height [cm]	BMI [kg/m^2]
1001001	23	M	White	Hispanic or Latino	81.1	180	25.0
1001002	65	F	Other: xxxxx	Not Hispanic or Latino	74.2	163	27.9

BMI = Body mass index
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_BAS

ACT-293987
Protocol: AC-065A309
Listing of baseline disease characteristics
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Date of initial PAH diagnosis	Months since initial diagnosis at baseline	Etiology of PAH	PAH associated with	Uptravi dose at screening [ug bid]	WHO functional class
1001001	ddMMMyyyy	xx.x	Idiopathic PAH		800	II
1001002	ddMMMyyyy	xx.x	PAH associated with	Connective tissue disease	1200	III

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_MH

ACT-293987
Protocol: AC-065A309
Listing of medical history
Analysis Set: Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	System Organ Class Preferred Term (Reported Term)	Start date	End date	Ongoing at Screening
1001001	xxxxxxxxxxxxxxxxxx XXXXXXXXXXXXXXX (XXX XXX XXXX)	ddMMMyyyy	ddMMMyyyy	
1001002	xxxxxxxxxxxxxxxxxx XXXXXXXXXXXXXXX (XXX XXX XXXX)	ddMMMyyyy		Yes

System Organ Classes and Preferred Terms are based on MedDRA version <xx.x>.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_CM

ACT-293987
Protocol: AC-065A309
<Title>
Analysis Set: Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	ATC Class Preferred Term (Reported Term)	Start date / Day	End date / Day	Start in Period	End in Period	Started prior to start of i.v. selexipag?	Ongoing at End of Study	Dose/Unit/Frequency/Indication/Route
1001001	xxxxxxxxxxxxxxxxxx XXXXXXXXXXXXXXX# [1] (XXX XXX XXXX)	ddMMMyyyy/xx	ddMMMyyyy/xx		1	Yes	No	25/mg/bid/XXXXXX/Oral
1001002	xxxxxxxxxxxxxxxxxx XXXXXXXXXXXXXXX (XXX XXX XXXX)	ddMMMyyyy/xx		FU		No	Yes	XXXX/XXX/XXXX/XXXXXX/XXXX

ATC Classes and Preferred Terms are based on WHO-DRUG dictionary version <xxx>.
PAH specific medication
[1] Previous therapy, [2] Ongoing therapy, [3] Study concomitant therapy
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas

L_EXP_PO

ACT-293987
Protocol: AC-065A309
Listing of Uptravi dosing records
Analysis Set: Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Time point	Uptravi administered	Date/time	Uptravi dose [ug]
1001001	Evening before Day 1		ddMMMyyyy/hh:mm	800
	Day 1 - Morning		ddMMMyyyy/hh:mm	800
	Day 1 - Evening		ddMMMyyyy/hh:mm	600
	Day 3 - Evening	No		
1001002				

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_EXP_IV

ACT-293987
Protocol: AC-065A309
Listing of study treatment dosing records
Analysis Set: i.v. Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Time point/ Visit	Start date/time	End date/time	Duration [min]	Concentration [ug/mL]	Infusion rate [mL/h]	Reason for change/end
1001001	Day 2 morning	ddMMMyyyy/hh:mm	ddMMMyyyy/hh:mm	xx	22.5	20	Infusion rate change
	Day 2 evening	ddMMMyyyy/hh:mm	ddMMMyyyy/hh:mm	xx	22.5	37.5	Temporarily interrupted due to an AE
	Day 3 morning	ddMMMyyyy/hh:mm	ddMMMyyyy/hh:mm	xx	22.5	20	Completed as per protocol
1001002	....						

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_COMP

ACT-293987
Protocol: AC-065A309
Listing of compliance with i.v. selexipag treatment
Analysis Set: i.v. Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Time point/ Visit	Planned dose [ug]	Actual dose [ug]	Compliance [%]
1001001	Day 2 morning	900	850	94.4
	Day 2 evening	900	870	96.7
	Day 3 morning	900	900	100.0
	Overall			97.0
1001002				

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_EG

ACT-293987
Protocol: AC-065A309
Listing of quantitative ECG measurements
Analysis Set: Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Visit / Time point	Date/time	Heart rate [bpm]	RR [ms]	PR [ms]	QRS [ms]	QT [ms]	QTcB [ms]	QTcF [ms]
1001002	Visit 2 - Day 1	ddMMMyyyy/hh:mm	xx*	xxx*	xxx*	xxx*	xxx*	xxx*	xxx*
	Unscheduled	ddMMMyyyy/hh:mm	xx	xxx	xxx	xxx	xxx	xxx	xxx
	Visit 2 - Day 2 IV-1 pre-dose	ddMMMyyyy/hh:mm	xx	xxx	xxx	xxx	xxx	xxx	xxx
	Visit 2 - Day 2 IV-1 post-dose	ddMMMyyyy/hh:mm	xx	xxx	xxx	xxx	xxx	xxx #	xxx
	Visit 2 - Day 2 IV-2 pre-dose	ddMMMyyyy/hh:mm	xx #	xxx	xxx #	xxx	xxx	xxx	xxx
	Visit 2 - Day 2 IV-2 post-dose	ddMMMyyyy/hh:mm	xx	xxx	xxx	xxx	xxx	xxx #	xxx
	Visit 2 - Day 3 IV-3 pre-dose	ddMMMyyyy/hh:mm	xx	xxx	xxx #	xxx	xxx	xxx	xxx
	Visit 2 - Day 3 IV-3 post-dose	ddMMMyyyy/hh:mm	xx	xxx	xxx	xxx	xxx	xxx	xxx
	Visit 3	ddMMMyyyy/hh:mm	xx	xxx	xxx	xxx	xxx	xxx	xxx

QTcB = QT interval Bazett's correction, QTcF = QT interval Fridericia's correction
* = Baseline, # = Marked abnormal value
Newly occurring or worsening post-baseline marked abnormalities are flagged.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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L_EG_QUAL

ACT-293987
Protocol: AC-065A309
Listing of qualitative ECG findings
Analysis Set: Safety Analysis Set

Country: <country>, Site: <Site number>

Subject number	Visit / Time point	Date/time	Interpretation	Findings
1001002	Visit 2 - Day 1	ddMMMyyyy/hh:mm	Normal	
	Unscheduled	ddMMMyyyy/hh:mm	Abnormal	XXXX
	Visit 2 - Day 2 IV-1 pre-dose	ddMMMyyyy/hh:mm	Normal	
	Visit 2 - Day 2 IV-1 post-dose	ddMMMyyyy/hh:mm	Normal	
	Visit 2 - Day 2 IV-2 pre-dose	ddMMMyyyy/hh:mm	Normal	
	Visit 2 - Day 2 IV-2 post-dose	ddMMMyyyy/hh:mm	Normal	
	Visit 2 - Day 3 IV-3 pre-dose	ddMMMyyyy/hh:mm	Normal	
	Visit 2 - Day 3 IV-3 post-dose	ddMMMyyyy/hh:mm	Normal	
	Visit 3	ddMMMyyyy/hh:mm	Normal	

Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: Layout may change with the structure of the data.

L_WHO

ACT-293987
Protocol: AC-065A309
Listing of WHO functional class
Analysis Set: Screened Analysis Set

Country: <country>, Site: <Site number>

Subject number	Visit	WHO functional class
1001003	Screening	II
	Visit 2 - Day 1	II*
	Visit 2 - Day 3	III
	Unscheduled	II
	Visit 3	I

* = Baseline
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

L_PK_CONC

ACT-293987
Protocol: AC-065A309
Listing of selexipag / ACT-333679 plasma concentrations
Analysis Set: Pharmacokinetic Analysis Set

Subject number	Visit	Timepoint	Selexipag concentration [ng/mL]	ACT-333679 concentration [ng/mL]
1001002	Visit 2 - Day 1	Pre-dose	xxx #	xxx #
		1 h post-dose	xxx	xxx
		2 h post-dose	xxx	xxx
		...		
	Visit 2 - Day 3	Pre-infusion start	xxx #	xxx #
		25 min post infusion start	xxx	xxx
		87 min post infusion start	xxx	xxx
		4 h post infusion start	xxx #	xxx #
		...		
1001003	...			

= Implausible plasma concentration
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
Page x of y

Programming note: List by subject. Only list subjects who provided data. Layout may change slightly depending upon data structure.

L_PK_DER

ACT-293987
Protocol: AC-065A309
Listing of derived PK parameters of selexipag and ACT-333679
Analysis Set: Pharmacokinetic Analysis Set

			i.v. selexipag			Uptravi			Ratio i.v. selexipag / Uptravi	
Parameter	Subject number	Time point	Dose [ug bid]	Selexipag	ACT-333679	Dose [ug bid]	Selexipag	ACT-333679	Selexipag	ACT-333679
Ctrough,ss [ng/mL]	1001002	Pre-dose	xxxx	xxx#	xxx#	xxx	xxx	xxx	xxx	xxx
		12 h post-dose	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	1001004	Pre-dose	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
		12 h post-dose	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Dose normalized Ctrough,ss,norm [ng/mL]	1001002	Pre-dose	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
		12 h post-dose	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Cmax,ss [ng/mL]	1001002		xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
....										
Dose normalized Cmax,ss,norm [ng/mL]	1001002			xxx	xxx		xxx	xxx	xxx	xxx
....										
AUCtau,ss [ng*h/mL]	1001002		xxxx	xxx#	xxx#	xxxx	xxx	xxx	xxx	xxx
....										
Dose normalized AUCtau,ss, norm [ng*h/mL]	1001002			xxx	xxx		xxx	xxx	xxx	xxx
....										
tmax,ss [h]	1001002		xxxx	xxx	xxx	xxx	xxx	xxx		
....										

= Obtained from implausible plasma concentration
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: List by parameter, then by subject. Do not display ratios for t_max.

L_PK_RATIO

ACT-293987
Protocol: AC-065A309
Listing of Cmax,ss and AUCtau,ss ratio of ACT-333679/selexipag
Analysis Set: Pharmacokinetic Analysis Set

Dose [ug bid]	Subject number	Cmax,ss Ratio ACT-333679/selexipag		AUCtau,ss Ratio ACT-333679/selexipag	
		Uptravi	i.v. selexipag	Uptravi	i.v. selexipag
200 ug b.i.d. p.o. / 225 ug b.i.d. i.v.	1001002	xxx	xxx	xxx#	xxx
	1001003	xxx	xxx	xxx	xxx
	1001005	xxx	xxx	xxx	xxx
400 ug b.i.d. p.o. / 450 ug b.i.d. i.v.	1001004	xxx	xxx	xxx	xxx
	1001010	xxx	xxx	xxx	xxx
...	1001006	xxx	xxx	xxx	xxx
Dose Normalized	1001002	xxx	xxx	xxx#	xxx
	1001003	xxx	xxx	xxx	xxx
	1001004	xxx	xxx	xxx	xxx
	1001005	xxx	xxx	xxx	xxx

= Obtained from at least one impalusible plasma concentration
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: List by dose, then by subject. Only list subjects who provided steady state data.

L_IMP_CONC

ACT-293987
Protocol: AC-065A309
Listing of selexipag concentration in the infusion solution
Analysis Set: Pharmacokinetic Analysis Set

Subject number	Visit / Time point	Selexipag concentration (eCRF) [ug]	Actual selexipag concentration [ug]
1001002	Visit 2 - Day 2 IV-1	xxx	xxx
	Visit 2 - Day 2 IV-2	xxx	xxx
	Visit 2 - Day 3 IV-3	xxx	xxx
1001003	Visit 2 - Day 2 IV-1	xxx	xxx
	Visit 2 - Day 2 IV-2	xxx	xxx
	Visit 2 - Day 3 IV-3	xxx	xxx
1001006			

Actual selexipag concentration was assessed using a validated liquid chromatography with UV detector assay.
Output: <Output name>, Produced by DATAMAP on ddMMMyyyy hh:mm (CET),
SDTM Date: ddMMMyyyy
Program: /<folder>/<program_name>.sas
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Programming note: List by subject. Only list subjects who provided data. Layout may change slightly depending upon data structure.

Appendix F Document history

Summarize the main changes and rationale for changes from one approved version to the next.

Version	Effective Date	Reason
1.0	22-May-2018	New
2.0	2-Jul-2018	Section 7.8.4: Implausible PK plasma concentrations will be identified by a PK specialist and flagged. PK parameters derived from implausible concentrations will be flagged as well. Flagged values will be listed but not included in summaries and statistical analyses. Section 5.4.5.1: Added Uptravi in list of PAH-specific therapies to be displayed in the tables. Section 8.2.2.4: Removed SAS code as this code will produce incorrect analysis (two-sample test / CI for median, while one-sample test / CI is appropriate). Section 8.2.3.3: Added j subscript for random intercept parameter for clarification of random parameter. Section 12.4.1: Added clarification that tables will be run on the SAF and only on the ivSAF if different from SAF to be consistent with Table 4. T_PK_EP_SUM: Removed ratio and CVb(%), as this information is contained in T_CV_MM. Listings L_EG, L_EG_QUAL, L_MH: General medical history and ECG are not collected for screen failures, thus population is changed from SCR to SAF. Corrections and additions to table shells to improve readability (e.g., date/time columns added, footnotes added)